

# COVID-19 revolution: a new challenge for the internist

## Management of COVID-19 in comorbidities

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### ABSTRACT

As the main title 'COVID-19 revolution: a new challenge for the internist' states, the global coronavirus infection disease 2019 (COVID-19) pandemic represented a new challenge for the internists. This paper is part of a series of articles written during the difficult period of the ongoing global pandemic and published all together in this fourth issue of the *Italian Journal of Medicine*, with the aim of sharing the direct experiences of those who were the first to face this severe emergency, expressing each point of view in the management of COVID-19 in relation to other diseases. Each article is therefore the result of many efforts and a joint collaboration between many colleagues from the Departments of Internal Medicine or Emergency Medicine of several Italian hospitals, engaged in the front line during the pandemic. These preliminary studies therefore cover diagnostic tools available to health care personnel, epidemiological reflections, possible new therapeutic approaches, discharge and reintegration procedures to daily life, the involvement of the disease not only in the lung, aspects related to various comorbidities, such as: coagulopathies, vasculitis, vitamin D deficiency, gender differences, etc.. The goal is to offer a perspective, as broad as possible, of everything that has been done to initially face the pandemic in its first phase and provide the tools for an increasingly better approach, in the hope of not arriving unprepared to a possible second wave.

This paper in particular deals with the management of COVID-19 in comorbidities.

The risk of severe coronavirus infection disease 2019 (COVID-19) disease and death is greater in subjects with comorbidities.<sup>1</sup>

The comorbidities, according to the current conceptualization, could be defined as *concordant* or *discordant*.

*Concordant*. Concordant comorbidities share the same overall pathophysiology and management of the main disease, whereas *discordant* comorbidities have no direct relationship with the main disease in either pathogenesis or management and do not share an underlying predisposing factor; moreover, the treatment for some of these discordant conditions might interfere with the treatment of the main disease.<sup>2</sup>

Below a list of the most frequent comorbidities, which could be all defined *discordant*, and some indications for their management during COVID time.

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### COVID-19 in patients with diabetes

Diabetes is one of the most frequent comorbidities associated to COVID-19 infection.

Epidemiological observations have pointed out that patients with diabetes have an increased risk of severe complications and fatal outcome from COVID-19 than those who do not have diabetes.<sup>3</sup> This finding is probably due to the high frequency of diabetes in older people, to its strong association with cardiovascular disease and to the increased risk of infections in people with diabetes.<sup>4</sup> As primary prevention strategy for COVID-19 disease, diabetic patients should try to optimize their metabolic control, staying hydrated and, when taken, continue with antihypertensive and lipid-lowering drugs.<sup>4</sup>

In case of COVID-19 disease, patients without diabetes but with high risk for metabolic disease must

be checked for the appearance of diabetes triggered by the virus.<sup>4</sup>

Patients with COVID-19 infection and diabetes must be intensely and reliably controlled, through the monitoring of plasma glucose, pH, electrolytes and blood ketones.<sup>4</sup>

In case of severe symptoms of COVID-19, it would be advisable to withhold sodium glucose cotransporter-2-inhibitors (SGLT-2 inhibitors) and metformin in order to reduce the risk of acute metabolic decompensation like ketoacidosis diabetic and lactic acidosis.<sup>5</sup>

In the absence of symptoms of COVID 19 or of a serious course of COVID-19 infection antidiabetic drugs like SGLT-2 inhibitor and metformin should not be stopped.<sup>4</sup>

If drugs are discontinued, the other therapeutic option is represented by insulin.<sup>5</sup>

Most patient will require doses of insulin higher than normal for the increased consumption due to the septic state; therefore a careful monitoring of fluid and potassium balance will be necessary.

Interestingly some cell studies have noted that the dipeptidyl peptidase-4 (DPP-4) enzyme, an usual pharmacological target in patients with diabetes, represent a receptor for the coronavirus responsible for Middle East respiratory syndrome.<sup>6</sup> Antibodies directed against DPP-4 enzyme are capable to inhibit primary cell infection by this virus.<sup>6</sup>

These statements lead to hypothesize the use of DPP-4 inhibitors as therapeutic option for COVID-19 infection, since they reduce DPP-4 concentrations and, as consequence, the infection of primary cell.<sup>7</sup>

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### COVID-19 in cancer patients

Cancer patients may be immunocompromised due to underlying malignancy or anticancer therapy.<sup>8</sup> In case of COVID-19 infection, cancer patients, especially those with hematological malignancy, leukopenia and those who receive antineoplastic treatment in the preceding 14 days of COVID-19 diagnosis, are at increased risk for serious events (hospitalization, need of mechanical ventilation, death) than the general population.<sup>9</sup>

It has been suggested that cancer patients should be screened for COVID-19 infection before the antineoplastic treatment and, in case of COVID-19 infection, immunosuppressants should be avoided or, at least, used with a reduced dose, until they are deemed medically clear.<sup>9</sup>

In order to avoid patients' exposure to medical departments, outpatient visits should be reduced; when possible, oral regimens should be preferred over intravenous ones; for example, for rectal cancer therapy fluorouracil can be replaced by oral capecitabine without any compromise of oncological outcome.<sup>8</sup>

A European, prospective, randomized, multicenter study, IMMUNONCOVID, is recruiting patients with COVID-19 infection and metastatic or advanced cancer, to compare the efficacy of tocilizumab, an interleukin-6 inhibitor, nivolumab, an anti-PD-1 and GNS561, a chloroquine analog.<sup>10</sup>

Regarding surgery, another key component of cancer management, it has been pointed out that patients who received surgery and concomitantly have been infected by COVID-19 have an increased risk of severe clinical events than those who did not experienced surgery.<sup>11</sup>

According to these findings, especially in case of early stage cancers, patients could be referred to neoadjuvant therapy and surgical intervention could be delayed without compromising the outcome.<sup>10</sup>

In case of radiation therapy (RT), if reasonable, hypofractionated schedules should be preferred.

In patients where RT significantly improves the survival chances, the treatment is the priority; conversely, in case of palliative RT a delay in treatment should be considered.<sup>12</sup>

Similarly, hematopoietic stem cell transplant (HSCT) patients are characterized by prolonged cytopenia, thus they have a high risk of various infections, especially respiratory viral infections, which are prevalent in both the pre- and the post-engraftment periods.

HSCT recipients should be evaluated closely and, if possible, the transplant should be deferred.<sup>13</sup>

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### COVID-19 in patients with cardiovascular diseases

The relationship between COVID-19 and cardiovascular conditions is very close: COVID-19 infection seems to be more severe in patients with cardiovascular comorbidities; severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may have a direct or indirect effect on myocardium, and finally, it can also interact with cardiovascular medications.<sup>14</sup>

A background of hypertension seems to correlate with severity of infection and mortality.

As observed with SARS-CoV, the internalization of virus into cells is realized through its spike protein binding to angiotensin-converting enzyme 2 (ACE-2).<sup>15</sup>

While in animal models it has been shown that ACE inhibitor and angiotensin receptor blockers can increase ACE-2 mRNA levels, there is no consistent evidence that the same happens in human tissues, therefore, to date, there is no justification to stop the RAS blockers therapy in patients with COVID-19 disease.<sup>16</sup>

It has been observed that statins could restore the reduction of ACE-2 induced by high lipids.

However, although the modulation of ACE-2 expression is associated with both infection and mortality rates in COVID-19, statins should not be

discontinued because of the long-term benefits.<sup>17</sup>

Vascular events seem to be a common complication of COVID infection.<sup>18</sup>

In case of acute coronary syndromes, the already well-coded strategies, invasive or not, remain valid for reperfusion treatment.<sup>18</sup>

An accurate medical history should be collected, assuming that every patient could be an asymptomatic SARS-CoV-2 carrier, and, at least patients with high clinical suspicion should be tested before the procedure.<sup>18</sup> When pursuing an invasive approach, appropriate personal protective equipment (*e.g.* gowns, face shield/goggles, N95 masks) and set-up (*e.g.* negative pressure room) must be available for the safety of healthcare workers and patients.<sup>18</sup>

Finally, it is necessary to remember that antiviral therapy for COVID-19 is associated with QTc prolongation, and, therefore, lopinavir/ritonavir and (hydroxy)chloroquine should be avoided in patients with congenital or acquired long QT syndrome.<sup>18</sup>

During treatment with these drugs patients must be monitored for the appearance of arrhythmias and particular care should be taken to prevent electrolyte disturbances.<sup>19</sup>

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### COVID-19 in patients with asthma and chronic obstructive pulmonary disease

Recent studies suggest that patients with severe or uncontrolled asthma and those with chronic obstructive pulmonary disease (COPD) seem to be at increased risk of a severe COVID-19 infection.<sup>20</sup> General recommendations for the management of these respiratory conditions remain valid and usual treatments must be continued in order to optimize disease control and reduce the risk of severe COVID-19 infection.<sup>20</sup>

SARS-CoV-2, as other viruses do, represents a trigger for asthma and COPD exacerbation, therefore a good control of underlying condition is needed.<sup>21</sup>

For patients with asthma in treatment with biologic drugs, current recommendations indicate to remain on them during this time.<sup>22</sup>

Despite the fact that oral steroids are not recommended to treat lung disease associated with COVID-19 for the possible increase in viral replication, they should still be administered to treat asthma exacerbations that respond poorly to bronchodilators.<sup>21</sup>

During the COVID-19 pandemic it would be advisable to limit and perform with caution lung function testing due the potential risk of virus aerosolization and infection transmission associated to the procedure.<sup>22</sup>

Nebulization should be avoided, if possible, and a metered-dose inhaler with a valved holding chamber or a dry powder inhaler (Turbuhaler™ or Diskus™) should be preferred, especially in health care settings.<sup>21</sup>

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### COVID-19 in patients with chronic renal failure

Dialysis patients constitute a population with high mortality due to COVID-19 infection since they combine older age, cardiovascular disease, diabetes, lung disease and impaired immune system with the need for dialysis treatment in healthcare settings.<sup>23</sup>

Several articles focusing on management of these patients have been released; according to an Italian proposed therapeutic management, in case of COVID-19 infection:<sup>24</sup>

- Asymptomatic or paucisymptomatic hemodialysis patients with negative chest X-ray should start anti-viral therapy, with any adjustment for kidney function, hydroxychloroquine 3/week, after every dialysis session and antibiotic therapy only in case of bacterial superinfection.<sup>24</sup>
- Asymptomatic or paucisymptomatic kidney transplant recipient with negative chest X-ray should stop their usual immunosuppressant therapy and started steroids (methylprednisolone 16 mg/die), in addition to start anti-viral therapy and hydroxychloroquine, adjusted for kidney function.<sup>24</sup>
- Hemodialysis patients and kidney transplant recipients who present severe symptoms and/or positive chest X-ray must be hospitalized. If necessary therapy with dexamethasone 20 mg/die for 5 days and tocilizumab should be started.<sup>24</sup>

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### COVID-19 in patients with inflammatory bowel disease

Patients with inflammatory bowel disease (IBD) are at risk of opportunistic infections, especially due to their immunosuppressive therapy.<sup>25</sup> Preliminary data suggest that IBD patients do not appear to be more susceptible to SARS-CoV-2 infection.<sup>26</sup>

An Italian prospective observational cohort study enrolled 79 patients with IBD and COVID-19 in order to detect their characteristics and outcomes.

This study demonstrated that, as well as in the general Italian population, age over 65 and presence of comorbidities are factors associated with worse outcome (pneumonia, hospitalization, need for respiratory assistance and death).<sup>26</sup>

Active IBD has been found to be significantly associated with a negative COVID-19 outcome, therefore IBD medication adherence should be encouraged.<sup>27</sup>

No increased risk of negative COVID-19 outcome related to the use of immunosuppressive drugs has been detected.<sup>26</sup>

In the development of COVID-19 acute respiratory distress an important role is played by the cytokine cascade, therefore it seems that patients on immunosup-

pressive treatment could be at lower risk of developing complicated SARS-CoV-2 complications.<sup>28</sup>

A trends towards statistical significance has been observed only for concomitant corticosteroid therapy; so, where possible, high dose systemic corticosteroids should be avoided.<sup>26,27</sup>

According to these findings, the International Organization for the Study of Inflammatory Bowel Disease (IOIBD) suggests, in absence of symptoms and test for SARS-CoV-2, to continue maintenance therapy, paying attention only to high doses of systemic corticosteroids (>20 mg/day prednisone or equivalent).<sup>29</sup>

The others recommendations made by IOIBD indicate in case of positive test for SARS-CoV-2 and absence of symptoms, to discontinue IBD therapies for a minimum of 10 days, and to resume therapy if no symptoms of COVID-19 appear; in case of positive test and presence of symptoms it is advisable discontinue IBD therapy.<sup>29</sup>

About the restart of therapy, two strategies have been identified, one symptom-based and one test-based.

According to the symptom-base strategy, IBD therapy could be resumed at least 10 days after COVID-19 symptoms onset and at least 3 days after resolution of fever without the use of fever-reducing medications plus improvement in respiratory symptoms. In severe COVID-19, a greater time frame from recovery may be appropriate.<sup>29</sup>

According to test-based strategy, the clinical parameters must be met, plus 2 consecutive negative nasopharyngeal or oropharyngeal COVID-19 molecular assays (real-time polymerase chain reaction or nucleic acid amplification tests swab specimens) collected >24 h apart.<sup>29</sup>

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