Short communication

Approach to patients with COVID-19 disease: the procedure in Udine.

Paolo Agostinis¹, Giulia Bontempo², Paola Della Siega², Valentina Gerussi², Alberto Pagotto¹, Emanuela Barbano³, Lucia Mazzoran³, Mario Calci³, Massimo Sponza⁴, Francesco Sbrana⁵, Stefano Fapranzi⁴, Aldo Baritussio⁶, Carlo Tascini².

¹U.O. Medicina Interna, Dipartimento di Medicina dell’Università di Udine – Università di Udine e Azienda Sanitaria Universitaria Integrata di Udine, Udine - Italia
²U.O. Malattie Infettive, Dipartimento di Medicina dell’Università di Udine – Università di Udine e Azienda Sanitaria Universitaria Integrata di Udine, Udine - Italia
³U.O. Medicina d’Urgenza, Dipartimento di Medicina dell’Università di Udine – Università di Udine e Azienda Sanitaria Universitaria Integrata di Udine, Udine - Italia
⁴U.O. Diagnostica Angiografica e Radiologia Interventistica, Dipartimento di Diagnostica per Immagini dell’Università di Udine – Università di Udine e Azienda Sanitaria Universitaria Integrata di Udine, Udine – Italia
⁵U.O. Lipoapheresis and Center for Inherited Dyslipidemias - Fondazione Toscana “Gabriele Monasterio”, Via Moruzzi, 1 - Pisa, Italy
⁶Ricercatore Senior, Università di Padova, Padova - Italia


SUMMARY

Coronavirus disease 2019 poses a serious threat to public health. The protocol developed at the Azienda Sanitaria Universitaria Friuli Centrale (Italy) is based on clinical data, laboratory tests, chest echography and HRCT. Several therapeutic options are considered, since patients vary in disease severity, evolution and co-morbidities and because so far there are no clear indications about therapeutic strategy based on randomized clinical trial. In this protocol chest echography has a central role in categorizing patient status, follow-up and decision-making.

Keywords: ARDS; Chest CT; COVID-19 disease; Infection control; Lung ultrasound; Outbreak; SARS-CoV-2.

Corresponding author: Francesco Sbrana, MD
Fondazione Toscana Gabriele Monasterio, Via Moruzzi, 1 - 56124 Pisa – ITALY;
Phone: +39 050 3152705; Fax: +39 050 315330; E-mail: francesco.sbrana@ftgm.it
Since December 2019, the outbreak of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 has posed a serious threat to global public health with a potentially fatal outcome in a significant part of the cases.

In Italy, Lombardy has been severely affected (Nacoti et al. 2020) and neighboring regions have organized themselves to deal with the COVID-19 outbreak. The aim of this paper is to present a protocol developed at the Azienda Sanitaria Universitaria del Friuli Centrale (North-East of Italy) to face the first wave of the epidemic.

**Case finding:** Patients admitted to the emergency room were identified on the basis of the following clinical features: fever, dry cough, lack of appetite, muscle pain, taste/smell changes, pneumonia, low finger oxygen saturation, positive walking test, diarrhea, sepsis, ARDS. Predisposing conditions (hypertension, diabetes, obesity, cardiac diseases, malignancy, male sex, nonsmokers) and history of contact with positive COVID-19 subject were also considered (Figure 1, panel A).

**Laboratory tests** at presentation: blood cell counting with differential, C reactive protein, procalcitonin, LDH, CPK, GOT, GPT, D-dimer, IL-6, ferritin; arterial blood gases (ABG); nasopharyngeal specimen for 2019-nCoV testing by RT-PCR; Pneumoplus® in excrete; search of Legionella and Pneumococcus antigens in urine; serology for HIV-1/2, HCV, HBV viruses; 12-lead electrocardiogram.

Typical findings were low white blood cells and platelet count, decreased percentage of lymphocytes, increased levels of C reactive protein, LDH, CPK, GOT, GPT, D-dimer, ferritin and IL-6. Normal procalcitonin. ABG revealed decreased PaO₂ and PaCO₂ in accordance with clinical severity.

**Thoracic imaging:** Chest CT identified lung involvement in symptomatic patients, regardless of the swab result and was helpful in patients with indeterminate clinic. Chest CT also informed about disease extension (Rubin et al. 2020; Colombi et al. 2020).

Lung ultrasound (US) was used for both initial categorization and follow up (Sofia et al. 2020): most frequent findings were B lines and small sub-pleural consolidations, also found in patients with normal RT-PCR or with normal chest XR. Other ultrasound findings were irregular and/or thickened pleural line, white lung areas alternating with normal lung (zebra sign) (Figure 1, panel B). Extension and increasing number of B lines, appearance of B lines in sub-clavicular regions, increasing diameter of consolidations were associated with increased risk of evolution towards ARDS and poor prognosis.

**Therapeutic protocol:** Patients were divided into three clinical classes:
• Mild disease: presence of fever, normal ABG, negative walking test, no US signs of lung involvement. These patients were discharged to home confinement, received hydroxychloroquine and azithromycin or antiretroviral drugs (according to ECG results) and were monitored by phone twice a day. They were admitted in COVID area in case of clinical worsening.

• Moderate disease: presence of fever, abnormal ABG, abnormal US. After high-resolution computed tomography (HRCT) of the chest, these patients were hospitalized in COVID structure, starting oxygen supplementation (Figure 2, panel A) and pharmacological treatment (Figure 2, panel B). Alarm criteria were respiratory rate >28/minute, worsening SpO\textsubscript{2}/FiO\textsubscript{2} or PaO\textsubscript{2}/FiO\textsubscript{2} ratio, extension of B lines and involvement of apical anterior areas. HRCT showed moderate-severe lung involvement.

In the presence of one of the alarm criteria, early CPAP treatment with helmet using low PEEP levels (5 - 10 mmHg) was started (NHS England 2020). If CPAP was not tolerated High Flow Nasal Cannula Oxygen Therapy was used (Alhazzani et al. 2020). To control the risk of transmission of the virus to health care workers (WHO 2020; Arulkumaran N et al. 2020) antiviral filters were installed on helmets and patients were treated in negative pressure rooms in the infectious diseases ward. Health care workers were regularly tested with nasopharyngeal specimen for 2019-nCoV by RT-PCR, and none has been reported positive to date.

• Severe disease: patients with severe respiratory insufficiency (PaO\textsubscript{2}/FiO\textsubscript{2} ratio <150) and/or ARDS were admitted in ICU. Patients with negative nasal swab and high suspicion of COVID-19 were isolated and further screened with lung US and HRCT to detect signs of COVID-19 disease. The nasal swab was repeated after 24 hours and coronavirus-19 was searched in sputum, bronchoalveolar lavage (BAL) or gastric aspirate (Wang W et al. 2020).

Drugs were administered based on severity of the clinical picture, evidence from clinical studies or, when that was lacking, evidence from experimental data, considering the profile of safety of the drug and possible interference with other drugs. Drugs administered in our unit included: chloroquine/azithromycin, antivirals (lopinavir/ritonavir, darunavir/cobicistat), immunomodulating agents (tocilizumab, steroids, ozone therapy), icatibant, amiodarone and anticoagulant therapy. The Italian Medical Agency initially approved the off-label use of Lopinavir/Ritonavir (or...
Darunavir in combination with Cobicistat or Ritonavir) and antimalarial chloroquine (or hydroxychloroquine - HCQ) in patients with SARS-CoV-2 infection (Agenzia Italiana del Farmaco 2020a). Subsequently, due to non-univocal clinical data in literature, their use was allowed only in clinical trials (Agenzia Italiana del Farmaco 2020b).

Amiodarone and chloroquine interfere with spike-protein processing, inhibiting the transfer of the viral genome in the cytoplasm of target cells.

Regarding dexamethasone, similar to ARDS, evidence has demonstrated the ability to down-regulate inflammation-coagulation-fibroproliferation and accelerate disease resolution (Villar J et al. 2020). Furthermore, this therapy was able to reduce 28-day mortality among hospitalized patients who were receiving either invasive mechanical ventilation or oxygen alone (RECOVERY Collaborative Group, et al. 2020).

Ozone therapy was used in case of overwhelming signs of inflammation (Ricevuti G et al. 2020; Tascini et al. 2020); tocilizumab, an antagonist of the interleukin-6 (IL-6) receptor, in patients with high level of IL-6 (Zhang C et al. 2020); icatibant, a selective competitive antagonist for the bradykinin B2 receptor, in patients with no response to previous treatments (van de Veerdonk F et al. Preprints 2020, van de Veerdonk F et al. JAMA Netw Open 2020).

Based on its efficacy in vitro on SARS-CoV1 infection, amiodarone was used when, in a deteriorating patient, all other drugs had not shown signs of efficacy (Stadler K et al. 2008; Lu CC et al. 2020; Aimo A et al. 2020).

Anticoagulant therapy with LMWH was administered in all patients with markedly elevated D-dimer (Tang N et al. 2020).

The antiviral agent remdesivir, antagonist of the interleukin-1 (IL-1) receptor, and immune globulin are proposed in severe and no responder cases (Spinner CD et al. 2020).

At Udine Hospital, 144 patients with COVID-19 infections were admitted as of 30th April 2020; the overall mortality has been 7% (13% in Italy).

The protocol here presented could be an example for the emergency room and COVID-19 ward during an overwhelming outbreak of COVID-19, trying to optimize available resources to obtain the best possible clinical outcomes and where chest echography has a central role in categorizing patient status, follow-up and decision-making.

**Conflicts of interest:** CT has received funds for speaking at symposia organized on behalf of Pfizer, Novartis, Merck and Astellas.
REFERENCES


Figure 1: Identification and management of patients with suspected SARS-CoV-2 infection. Panel A depicts the patient’s screening algorithm. Panel B shows thoracic echo panels.
Figure 2: Therapeutic protocol for patients with COVID-19 disease, oxygen therapy (panel A) and pharmacological treatment (panel B).