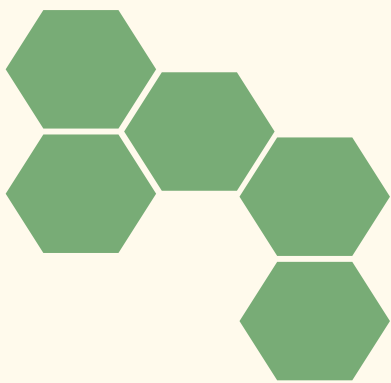




# **PATIENT SAFETY RECOMMENDATIONS FOR COVID-19 EPIDEMIC OUTBREAK**

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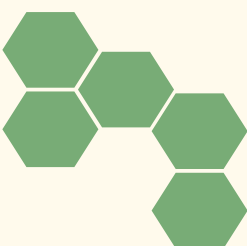
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# INTRODUCTION

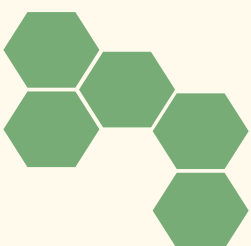
On the basis of reports and questions forwarded to the Clinical Risk Managers of the Italian Network for Health Safety (INSH) from physicians working on the front line, a series of recommendations have been developed referring to documents and papers published by national institutions (ISS) and Italian and international scientific societies and journals.

We have arranged the process to describe organising the work system according to the SEIPS Human Factors approach <sup>(1)</sup>.

1. Assess the work system
  - Team and organisation culture and communication
  - Environment
  - Tasks required and skills to complete tasks
  - Equipment for patient care and to protect staff
  - The people needed to provide care
  - The patients who will receive care
2. Develop reliable processes of care
3. Measure the outcomes of care

The document is work in progress and will be subject to updates by all professionals on a continuing basis. We appreciate and welcome the contribution of all those involved in COVID-19, both providers of care and patients who have received care.

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# 1.

## GENERAL RECOMMENDATIONS

### BUILDING THE TEAM

(including communication and team culture)

1. Emergency task-force should be promptly activated with a clear chain of command, roles and responsibilities, reliable information sharing tools and proactive approach.
2. Check frequently every day the communications sent by your institutions. Read carefully and respect them. Alternatively, print and make such communication available in the ward and share such information during handovers.
3. Clinical risk management units can support dissemination of documents, guidelines issued by the national/regional institutions for supporting the emergency management, relatively for measures of prevention to be taken. *Knowledge about Coronavirus transmission and spreading and clinical characteristics of related disease (COVID-19) are constantly evolving, so that indications for clinical practice change frequently, i.e. case or suspicion definition, criteria for making tampons, etc.*
4. The clinical risk management units must keep contact with front line workers and provide support. The reporting of adverse events must occur within the task-force activity and be primarily related to the core activities in time of pandemic. Secondly, the reporting of Adverse Events should be encouraged in order to maintain the underpinning safety climate

in order to promote, whenever possible, prompt corrective and improvement actions. Consider quick reporting tools such as confidential instant messages (IM) or audio-messages.

5. The clinical risk management units should also receive evidence of good practice so this can be disseminated.

### TASKS TO BE UNDERTAKEN AND SKILLS REQUIRED

1. Organise brief educational training on the correct use of medical and protective devices targeted to all healthcare workers and develop video tutorials to be available on the healthcare trust website.
2. Hold refresher courses on hand-hygiene, the prevention of VAP (Ventilator Associated Pneumonia) and CLABSI (Central Line Associated Bacterial Infection), bundles and the SEPSIS bundle for early sepsis recognition and management to all healthcare workers <sup>(2)</sup>, but in particular to the staff not in the frontline of the emergency who could be called as replacements.
3. Organise early support of expert doctors/nurses with young or colleagues from other specialties who may be called upon to replace them to properly educate them.
4. Do not forget appropriate instructions for environment disinfection (detergents, contact time, frequency) to cleaners <sup>(3)</sup>.

# 1.

## GENERAL RECOMMENDATIONS

### EQUIPMENT NEEDED TO PROTECT STAFF

1. Contact and droplet precautions can be used in routine patient care of patients with suspected or confirmed COVID-19 <sup>(4)</sup>.
2. Contact and airborne precautions are recommended when performing aerosol generating procedures (AGPs), including intubation and bronchoscopy <sup>(4)</sup>.
3. Prevent biosafety precautions shortage by extended use and limited re-use of full-face shields and disposable facial filtering masks <sup>(5)</sup>, by identifying a priority order to the different wards and by supply of reusable tyvek suits. Store such devices in a locked or secured area and distribute to staff appropriately <sup>(5)</sup>. *The infection spreads so quickly that a depletion of reserve medical supplies is mandatory.*

### EQUIPMENT NEEDED TO TREAT PATIENTS

1. Give any patient seeking for medical assistance, independently from symptoms, a surgical mask to put on, at their first contact with healthcare services <sup>(6)</sup>.
2. In the dedicated care areas for patients with COVID-19, ensure that:
  - a. haemo-gas analyzers;
  - b. pulse oximeters;
  - c. oxygen therapy;
  - d. ventilator therapy equipment and suction pumpsare available and well functioning <sup>(7)</sup>.

### ENVIRONMENT

1. Strictly apply, without exceptions, the indications for disinfection of environments and tools (sodium hypochlorite at 0.5% or 70% ethyl alcohol solution) <sup>(8)</sup>. *It is not yet well known how long the virus resists in the environment, but it is inactivated by solutions based on hypochlorite and alcohol.*
2. Prevent germicide deficiency by using galenic preparations.
3. Keep in mind that the creation of dedicated hospitals may divert from the emergencies / emergencies network. Evaluate carefully the fallout of the timing of treatment decisions for time-dependent diseases. Consider the use of underused or quiescent equipped hospitals to meet this need.
4. Unless activity is suspended, in the outpatient (public or private) clinics:
  - a. avoid gatherings in waiting rooms (recommend people wait outside, respecting the distance of at least 1m between seats);
  - b. inform symptomatic subjects with fever and / or cough and / or dyspnea not to go to clinics;
  - c. disseminate hygiene and health standards recommendations in the waiting room.

### PATIENTS

1. Reduce hospital admissions, routine outpatient clinic appointments and routine surgical procedures and regulate hospital visits.

# 1.

## GENERAL RECOMMENDATIONS

*Even in absence of strong evidence, it would be a good practice for authorized family members to enter the wards wearing medical masks, due to patients' frailty.*

2. In the full-blown epidemic phase:
  - a. consider all patients with flu-like symptoms who access hospitals as potentially affected until proven otherwise (2 negative swabs at least 48-72h apart);
  - b. isolate, if structurally possible, suspected or confirmed patients with COVID-19 in single rooms in dedicated hospitals (Covid-Hospitals) or buildings;
  - c. create separate unclean/clean paths, even with the help of external mobile structures (curtains);
  - d. Use a screening interview to identify suspected cases before admission to the examination room in case of infection symptoms or to healthcare services for other reasons (i.e. surgery, coronary angioplasty, labour and delivery, etc.):
    - if the criteria of case or suspicion are met, refer the patient for evaluation, according to local procedures;
    - general practitioners will provide their patients with useful information by social networks, email or other tools and keep them updated.
3. Contacts of Covid-19 positive patients should be taken on charge by local Public Health Services for epidemiological purposes and

active surveillance and clinically evaluated in the locally designated sites, only if symptomatic.

4. Use broad case definitions and intensive testing strategies: it allows the epidemic outbreak to be circumscribed earlier and better.

*Aggressive contact tracing and intensive testing along with home isolation have been a winning strategy in some Italian regions such as Veneto and in Asian countries <sup>(61)</sup>. The value of the epidemiological link as an essential criterion for case definition is scarce in a globalized world.*

# 2.

## RE-ORGANIZATION OF EMERGENCY NURSING STAFF IN COVID-19

(77, 78,79)

1. Define the maximum number of intensive care, subintensive and ordinary hospital beds that can be retrieved and activated within the organization and an incremental activation plan (e.g. conversion of operating rooms and sub-intensive areas into intensive care, recovery of unused hospitals) and consequently define the number of nursing staff needed at each step.
2. Make every effort to ensure numerically and professionally expert assistance in relation to beds increase.  
*The beds can be increased with less or greater economic commitment, greater or lesser time interval, the real limited resource is the human one, in terms of specialized skills that cannot be improvised.*
3. Alternatively, increase the number of nurses, but providing for a constant number of nurses who are experts in intensive care in each shift.  
*The Society of Critical Care Medicines encourages hospitals to adopt a tiered strategy of distribution of personnel in pandemic conditions. Telemedicine can be an aid to be used to connect expert professionals with nursing homes (79).*
4. Consider the following recovery criteria for intensive care:
  - a. previous service in intensive care;
  - b. current or previous service in the operating room;
  - c. current or previous service in specialized intensive care (e.g. cardiology intensive care);
  - d. lastly, certified training (e.g. master) even without experience, in intensive care.
5. Use similar principles for sub-intensive respiratory units, where non-invasive mechanical ventilation is practiced.
6. Recall retired experienced staff.
7. Quickly activate multiple channels for nursing staff recruitment, favoring the new hiring of staff with previous experience (especially in intensive and sub intensive care units).
8. Caution should be used when introducing young graduates to the areas most exposed to the emergency.

# 3.

## RECOMMENDATIONS FOR DIAGNOSIS

1. The adequate specimen for Real Time-Polymerase Chain Reaction (RT-PCR) testing is nasopharyngeal and oropharyngeal sampling. Prefer lower respiratory tract (LRT; expectorated sputum, endotracheal aspirate, or bronchoalveolar lavage) when readily available (for example, in mechanically ventilated patients) <sup>(2)</sup>. Quality of RT-PCR testing is a crucial issue. Both pre-analytical and analytical variables should be carefully taken into account and a validation process should be performed according to ISO 15189 (3 protocols) <sup>(9)</sup>.
2. The determination of anti-SARS-CoV2 IgG and IgM antibodies can be useful in the diagnostic confirmation of patients with clinical, biochemical and/or instrumental characteristics of COVID-19, but repeatedly negative RT-PCR, beyond population epidemiological studies. Keep in mind, however, there are different techniques with different levels of sensitivity and specificity, that the IgM are detectable 7-10 days after the onset of symptoms and the IgG not earlier than 12 days and that the viral load gradually decreases with increasing serum antibody levels. Diagnosis is confirmed if it is observed seroconversion from IgM to IgG or an increase in the IgG titer 4 or more times between the first and second determination <sup>(81)</sup>.
3. Many of the most common symptoms of novel coronavirus

disease (Covid-19) are similar to those of common flu or cold. So, it is also suggested knowing which common symptoms of flu or cold are not symptoms of COVID-19. COVID-19 infection seems to rarely cause a runny nose <sup>(10)</sup>.

*Rhinorrhea ("runny nose") is not a symptom of Covid-19 and nasal congestion ("stuffy nose") is reported only by 4.8% of patients.*

4. The most common Covid-19 symptoms are: fever (88%), dry-cough (68%), fatigue (38%), thick sputum production (34%), shortness of breath (19%), arthromyalgia (15%), sore throat (14%), headache (13.6%), chills (11%), nausea/vomiting (5%), nasal congestion (4.8%), diarrhea (3.7%). <sup>(11)</sup>  
*Data from a series of 55,924 laboratory confirmed cases of COVID-19 in China in the period up to February 2020 <sup>(11)</sup>.*
5. Acute alterations of taste and olfact are COVID-19 symptoms.  
*A multicentric European study including over 400 subjects reported such symptoms in over 85% of cases <sup>(12)</sup>.*
6. Beware of patients with gastrointestinal symptoms.  
*Nausea / vomiting and / or diarrhea can be present in about 9% of cases <sup>(11)</sup>. These symptoms have so far been one of the most frequent causes of omission or diagnostic delays.*
7. Atypical clinical manifestations reported in the literature are: syncope due to orthostatic hypotension, testicular pain, hemoptysis, headache, dizziness, altered mental state.



# 3.

## RECOMMENDATIONS FOR DIAGNOSIS

In particular, cases of Guillain-Barré Syndrome or its variant with involvement of the cranial nerves [Miller Fisher syndrome (ataxia, areflexia, ophthalmoplegia)], meningoencephalitis, cranial polyneuritis, acute cerebrovascular events have been described <sup>(62,67)</sup>.

*Keeping in mind these symptoms is important to not incur diagnostic errors and / or dangerous exposures of healthcare professionals and other patients, when present in isolated form.*

8. Cardiovascular manifestations of Covid-19 are: non-specific myocardial damage, myocarditis, myocardial infarction, arrhythmias, pulmonary embolism and heart failure, cardiogenic shock and cardiac arrest. Acute heart failure has been described as the first manifestation in 23% of cases and palpitations in 7%.

*These manifestations may be due to the direct effect of the virus, the systemic inflammatory response, hypoxia, coagulopathy, but also to the effect of the drugs used. The presence of these manifestations aggravates the prognosis as well as the presence of pre-existing heart disease <sup>(68,69)</sup>.*

9. Pay attention to the relationships of COVID-19 with arterial (stroke, IMA) and venous thrombotic events (VTE), as well as the negative impact on these events in COVID-19 and non-COVID patients.

*The lockdown and the fear of contagion have reduced the use of hospital for pathologies other than COVID-19, even acute. The infection is associated with a more severe prognosis in subjects with stroke. Virus-induced coagulopathy and / or systemic*

*inflammatory response can promote thrombotic and even bleeding events, in the case of DIC. The fear of a negative interaction between infection and the use of NSAIDs has led some patients to discontinue ASA. Antivirals, such as lopinavir/ritonavir reduce the effect of antiplatelet agents such as clopidogrel and enhance that of ticagrelor. The burden of VTE is increased by the diagnostic difficulty (hypoxia and increased d-dimer are already part of the clinical picture of COVID-19; difficulty in performing angio-CT, echocardiogram and echocolor Doppler in prone patients). Diagnostic tips for VTE can be signs of deep vein thrombosis, hypoxia disproportionate to the lung picture, acute deterioration of the right ventricular function <sup>(68-69)</sup>.*

10. Vital parameters measurement (respiratory rate and peripheral saturation O<sub>2</sub> in ambient air, SpO<sub>2</sub> are recommended) and walking test are fundamental to monitor patients managed at home. In addition, it is recommended to perform a blood gas analysis in ambient air if SpO<sub>2</sub> <94%, at triage or as soon as possible, for those who come to the hospital <sup>(13,14)</sup>.
11. Do not rely only on PO<sub>2</sub> <60 for the diagnosis of respiratory failure, always calculate the P/F, especially in young subjects.
12. Define a "COVID-19 profile" for the rapid order entry of blood tests, including the following tests: blood count, C-RP, creatinine, blood glucose, albumin, AST ALT, bilirubin, pneumococcal and legionella urinary agents, PT-INR, troponin and procalcitonin.
13. Chest X-rays have limited sensitivity in

# 3.

## RECOMMENDATIONS FOR DIAGNOSIS

early stages of Covid-19 pneumonia. CT scan is more sensitive, but raises logistical problems. If ultrasounds competencies are available, use chest US, but disinfect US probes after contact with every Covid-19 suspected patient <sup>(15)</sup>.

14. Monolateral lung infiltrates do not exclude COVID-19.

*They have been described in 25% of cases <sup>(15)</sup>.*

15. The most common reported laboratory abnormalities in Covid-19 patients are: Lymphopenia (35-75%), increased C-RP (75-93%), LDH (27-92%), ESR (up to 85% of cases), hypoalbuminemia (50-98%) and anemia (41-50%).

*Data from a systematic revision of literature <sup>(16)</sup>.*

16. The following negative prognostic factors have been reported: leukocytosis, neutrophilia, increased procalcitonin, LDH, AST, ALT, total bilirubin, creatinine, troponin, d-dimer, PT and hypoalbuminemia, lymphopenia. Even thrombocytopenia is associated with severe disease <sup>(16, 17)</sup>.

*Severe lymphopenia and lymphocytes count fall during the first 4 days since hospital admissions have been associated with a higher mortality. Increased white blood cell count, neutrophil count and procalcitonin could reflect bacterial superinfection, while increased d-dimer and PT a diffuse intravascular coagulation (DIC), reported in up to 75% of patients who died <sup>(16)</sup>.*

17. History of smoking, older age, comorbidities, respiratory failure, maximum body temperature on admission  $\geq 37.3^{\circ}\text{C}$ , albuminemia  $< 4$

mg/dl, higher SOFA score, d-dimer  $> 1000\text{ng/ml}$  would be risk factors for disease progression (severe or critical disease/death) <sup>(18, 70)</sup>.

18. Do not forget other respiratory infections (legionella, pneumococcus, mycoplasma, chlamydia, other respiratory viruses) even if during epidemics, so look for other pathogens and consider antibiotics.

*During epidemics it is important to avoid availability bias that means diagnose all infections due to epidemic agents. Further, WHO recommends investigating other pathogens, as co-infections have been reported <sup>(2)</sup>.*

19. Use disease severity stratification for the choice of the treatment setting (home, ordinary, sub-intensive or intensive care unit). WHO distinguishes 6 clinical syndromes associated with COVID-19: uncomplicated disease, mild pneumonia, severe pneumonia, ARDS, sepsis and septic shock. Patients with uncomplicated upper respiratory tract viral infection, may have non-specific symptoms such as fever, cough, sore throat, nasal congestion, malaise, headache, muscle pain or malaise. These patients do not have any signs of dehydration, sepsis or shortness of breath and can be treated at home <sup>(2)</sup>.

20. Pay attention to elderly people and immunocompromised subjects as they can present vague and/or atypical symptoms <sup>(2)</sup>.

21. Immediately notify the Public Health Officials of Covid-19 positive patients (use infectious disease notification forms) <sup>(19)</sup>.

# 4.

## RECOMMENDATIONS FOR HOSPITAL TREATMENT

1. Before prescribing antiviral drugs, verify drug-drug and drug-disease interactions, pay particular attention to oral anticoagulants that could be substituted by low molecular weight heparin.

*Current antiviral therapy schemes include drugs such as lopinavir/ritonavir, chloroquine or hydroxychloroquine, darunavir, cobicistat, tocilizumab, remdesivir<sup>(14, 20)</sup> which present interactions with antibiotics, antiarrhythmics, statins, anti-angina, etc. (table 1, 2, 3, 4).*

2. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are safe and should not be discontinued during Coronavirus epidemics<sup>(21)</sup>.
3. There is no proof that ibuprofen can aggravate Covid-19 clinical picture and the European Medicines Agency is monitoring this issue<sup>(22)</sup>.
4. Beware of the concomitant presence of antiphospholipid antibody syndrome, porphyria, myasthenia gravis and favism (possibly G6PDH dosage), before prescribing chloroquine or hydroxychloroquine.
5. Start oxygen therapy at 5 L/min and titrate flow rates to reach SpO<sub>2</sub> ≥90% in non-pregnant adults and SpO<sub>2</sub> ≥92-95 % in pregnant patients<sup>(2)</sup>.
6. High-flow nasal oxygen (HFNO) or non-invasive ventilation (NIV) should only be used in selected patients with hypoxemic respiratory failure (P/F next to 300 for HFNO and 250-300

for NIV), but with alerts and with preserved ventilator dynamics. Monitor closely for clinical deterioration<sup>(7, 23)</sup>.

7. Do not prolong HFNO or NIV for over 2 hours in the case of failure to improve (HFNO: respiratory rate ≥24/min, NIV: respiratory rate ≥28/min and/or worsening P/F for both<sup>(7, 23)</sup>. *High flow nasal cannulas and non-invasive ventilation are not recommended in viral pandemics, based on studies conducted in influenza and MERS<sup>(2)</sup>.*
8. Avoid nebulisation therapies for the potential spread of pathogens. *Nebulisers generate aerosol particles that can carry bacteria and viruses deep into the lung. The risk of infection transmission may increase with nebulisers as they can generate a high volume of respiratory aerosols that may be propelled over a longer distance than in natural dispersion patterns. Nevertheless, the larger particles may cause cough in both patients' and bystanders' and increase the risk of spreading the disease. So, nebulisers in patients with pandemic COVID-19 infection have the potential to transmit potentially viable COVID-19 to susceptible bystander hosts<sup>(24)</sup>.*
9. Administer intravenous fluids only if needed and avoid steroids, unless for other indications. *Excessive fluid administration could aggravate oxygenation and be dangerous, especially in settings where mechanical ventilation is not readily available. Steroids were not associated with benefits, but rather with damage in the 2003 SARS epidemic and a delay in virus clearance in Middle-Eastern Respiratory Syndrome (MERS) of 2012<sup>(2)</sup>.*
10. Assess thromboembolism and bleeding risk

# 4.

## RECOMMENDATIONS FOR HOSPITAL TREATMENT

of every patient and provide appropriate thromboprophylaxis.

*Consider that recovery times and therefore hypomobility of a subject with COVID-19 are long (at least 15 days in mild forms and up to 6 weeks in severe/critical ones) and diffuse intravascular coagulation (DIC) can complicate the course* <sup>(2, 15)</sup>.

11. Consider pharmacological and non-pharmacological prophylaxis (mobilization and hydration) of venous thromboembolism, depending on the bleeding risk, also in patients managed at home or discharged from the hospital, if they have additional risk factors (eg cancer, bedding, previous VTE, ecc.) <sup>(68)</sup>.
12. Low molecular weight heparins represent the anticoagulants of choice in COVID-19. For reasons of manageability, compatibility and risk of exposure of healthcare professionals, unfractionated heparin should be reserved for patients with severe renal failure or candidates to invasive procedures <sup>(68)</sup>.
13. Respiratory rate, peripheral oxygen saturation (SpO<sub>2</sub>) and arterial blood gas analysis results must be monitored closely during hospital stay due to insidious presentation of severe hypoxemia in this disease. Intra-arterial radial catheters insertion is to be considered to reduce arterial punctures, even outside ICU.
14. Also monitor white blood cells, lymphocytes and platelets count, LDH, procalcitonin and d-dimer are considered alarm flags <sup>(13, 15, 17)</sup>.
15. Be aware of an eventual development of severe form around 7 days after symptom onset <sup>(13)</sup>.
16. If a patient reports a SpO<sub>2</sub> ≤90% in free air or ≤92% in COT and /or presents FOR ≥30 acts/min and/or severe respiratory distress, intensive care therapist consultation must be required <sup>(25)</sup>.
17. Use biosafety precautions when handling oxygen therapy devices <sup>(23)</sup>; cover the patient's face with a surgical mask during HFNO or C-PAP <sup>(23)</sup>; to reduce the risk of aerosolization, possibly use a dual or single circuit non-invasive ventilator with an integrated expiratory valve and the helmet as interface <sup>(7)</sup>.

# 5.

## ETHICS OF TREATMENT DECISIONS

This is a complex issue which will be decided upon in the local setting as per previous ethical frameworks.

We recommend that the ethical decision making process be developed in anticipation of making complex decisions, rather than in reaction to the need to make a decision

With regard to management of the patient affected by COVID-19 in intensive care, we offer a number of references which will assist in developing the local ethical guidelines <sup>(25, 26, 27, 28)</sup>. Other important publications (not included among references):

Giacomo Grasselli, Antonio Pesenti, Maurizio Cecconi. Critical Care Utilization for the COVID-19 Outbreak in Lombardy, Italy Early Experience and Forecast During an Emergency Response. JAMA published online March 2020

<https://jamanetwork.com/journals/jama/fullarticle/2763188>

Robert D. Truog, Christine Mitchell and George Q. Daley, Robert D. Truog., Christine Mitchell, George Q. Daley.. The Toughest Triage — Allocating Ventilators in a Pandemic This article was published on March 23, 2020, at NEJM.org.

<https://www.nejm.org/doi/pdf/10.1056/>

[NEJMp2005689?listPDF=true](https://www.nejm.org/doi/pdf/10.1056/NEJMp2005689?listPDF=true)

Ethical Framework for Health Care Institutions Responding to Novel Coronavirus SARS-CoV-2 (COVID-19) Guidelines for Institutional Ethics Services Responding to COVID-19 Managing Uncertainty, Safeguarding Communities, Guiding Practice  
Hastings Institute

<https://www.thehastingscenter.org/wpcontent/uploads/HastingsCenterCovidFramework2020.pdf>

# 6.

## RECOMMENDATIONS FOR SURGERY

These recommendations apply to the medical staff of the operating blocks in case of COVID-19.

1. An operating room maintained at negative pressure with a high frequency air exchanges (at least 25 cycles/h) or designated 'contaminated' surgery-only is sensible <sup>(71)</sup>.
2. Surgical patients suspected or positive for SARS-CoV-2 infections should follow the local management protocol, which may include:
  - wearing specified bracelets and surgical masks;
  - having their medical records marked with warning labels;
  - being brought through defined routes and lifts to the special isolation area for recovery <sup>(72)</sup>.
3. A dedicated portable ventilator should be used when managing infected ICU patients, switching off the gas flow and closing the endotracheal tube to reduce aerosol production when connecting to the operating room ventilator. The gas sampling tube should be protected by a high-efficiency particulate air (HEPA) filter and the soda lime should be changed regularly <sup>(73)</sup>. Anaesthetists should use level 3 protective measures and connect HEPA filters on both limbs of the circuit and consider disposable components <sup>(73)</sup>.
4. Surgeons and personnel not needed for intubation

should remain outside the operating room until anesthesia induction/recovery and intubation/extubation are completed by the anesthesiologist. (Minimum time before the entrance of the surgical team depends on the type of PPE and the characteristics of the room - refer to the local indications).

5. Patients with COVID-19 may need to undergo emergency and/or emergency surgery. The following recommendations should be observed <sup>(29, 30, 31)</sup>.

### ASYMPTOMATIC COVID-19 POSITIVE PATIENT

- Surgical team wears the surgical mask, together with the complete dressing required for ordinary operations.
- Patient wears the surgical mask until the intubation procedure (I.O.T.).
- FFP2/FFP3 masks only for anesthesiologist and/or nurse assigned to anesthesiological assistance.
- Patient's airways protected with TNT light drapes compatible with anesthesiological assistance.
- Minimal incisions for trocars placement (using balloon trocar, if available).
- Evacuation of all smoke before the specimen extraction.
- Closed smoke suction system with ultra-low particulate arrestance filter (ULPA).

# 6.

## RECOMMENDATIONS FOR SURGERY

### PAUCISYMPTOMATIC COVID-19 POSITIVE PATIENTS

- Surgical team wears a mask with FFP2 / FFP3 filter.
- Patient wears the surgical mask until the I.O.T.
- FFP2/FFP3 masks only for anesthesiologist and/or nurse assigned to anesthesiological assistance.
- Patient's airways protected with TNT light drapes compatible with anesthesiological assistance.

### SYMPTOMATIC COVID-19 POSITIVE PATIENTS

- FFP2/FFP3 masks for all staff in the operating room.

Protection level of the surgical gowns depends on the type of procedure. Level 4 is the highest fluid and microbial barrier, and is needed for long, fluid-intensive procedures; level 3 is indicated as a moderate fluid barrier protection<sup>(74)</sup>.

6. The number of healthcare professionals present during the procedure should be limited to only those essential for patient care and procedure support (no visitors or observers allowed, no teaching/academic activities).
7. Consider laparoscopic approach only after strict evaluation of risk/benefit for both patient and staff. Precautions during laparoscopic surgery may include:
  - lower intra-abdominal CO<sub>2</sub> pressure;

### COVID-19

- closed smoke suction system with ultra-low particulate arrestance filter (ULPA);
  - minimal incisions for trocars placement (using balloon trocar, if available);
  - evacuation of all smoke before the specimen extraction.
8. Identify explicit priority criteria for elective surgical interventions to be performed even during an emergency (e.g. oncological interventions at high risk of progression or complication)<sup>(75)</sup>.
  9. It is recommended to perform a sanitization and disinfection for at least 1 hour, at the end of the intervention.
  10. Team working organisation.

Surgical teams in order to stay healthy and maintain continuity of care should divide into teams of senior and junior doctors and work for a 2 week period. After the 2 weeks, teams will come in to release the other. This will allow easier replacement of team members should they fall ill and potential containment of the virus to smaller staff numbers and an ability to maintain some service provision and clinical care.

11. It is recommended to dispose all the operating material through the special waste route and to use disposable material/TNT.

# 7.

## RECOMMENDATIONS FOR PREGNANT WOMEN

1. Reduce access of pregnant women to prenatal care, limiting only to high-risk cases <sup>(32)</sup>.

*There is no evidence of an increased risk of unfavorable maternal or fetal outcomes in the case of Covid-19. However, evidence relating to influenza and SARS-COV1 must induce to consider the pregnant woman as a high risk patient.*

2. Infants born to mothers with confirmed COVID-19 should be considered as suspects. As such, these infants should be isolated from others <sup>(33)</sup>.
3. Separation (i.e. in an individual room) of the infant from the mother with Covid-19 confirmed or suspected, until the precautions based on the transmission risk of the mother are suspended. The decision should be discussed carefully between the caring team and the mother, evaluating risk and benefits of this choice, including the protective potential of colostrum, breast milk and feeding time <sup>(32,33)</sup>.
4. The discharge of mothers after childbirth must follow the recommendations for discharge of Covid-19 or suspected patients <sup>(32)</sup>.
5. In the case of a woman with suspected SARS-CoV-2 infection or with COVID-19, according to her clinical conditions and desire, breastfeeding should be started and / or maintained directly on the breast or with squeezed breast milk <sup>(33)</sup>. If mother and child must be temporarily separated because

of mother clinical conditions, one should help the mother to maintain milk production through manual or mechanical/electric squeezing <sup>(33)</sup>.

*In a limited series reported to date, the presence of the virus in the breast milk of infected women has not been reported, but anti-SARS-cov2 antibodies have been found <sup>(32)</sup>. So breast milk would be protective.*

6. A mother with confirmed COVID-19 or ongoing swab samples because symptomatic should take all possible precautions to avoid spreading the virus to the baby, including washing hands before touching the baby and wearing a face mask, if possible. during breastfeeding. If using a manual or electric
7. The decision to proceed to a pre-term birth is based on many factors: gestational age, maternal conditions and fetal stability and requires a collegial evaluation by obstetric, neonatal and intensive care specialists (depending on the mother's condition) breast pump, the mother must wash her hands before touching the breast pump or parts of the bottle. If possible, have another person administer the milk to the baby <sup>(33)</sup>. *It is not yet known whether COVID-19 can be transmitted through breast milk. At present, the main concern is not whether the virus can be transmitted through breast milk, but rather whether an infected mother can transmit the virus through respiratory droplets during breastfeeding <sup>(32)</sup>.*
8. For assisting the delivery of women with confirmed or suspected Covid-19, staff must use the safety precautions provided for non-



# 7.

## RECOMMENDATIONS FOR PREGNANT WOMEN

pregnant patients<sup>(33)</sup>.

9. Pregnant women with suspected or confirmed SARS-COV2 infection should be treated with supportive therapies, however taking into account the physiological characteristics of pregnancy<sup>(2)</sup>.
10. The use of experimental therapeutic agents outside of a research study should be guided by an individual risk-benefit analysis based on the potential benefit to the mother and the safety of the fetus, with the consultation of an obstetrician specialist and an ethics committee<sup>(2)</sup>.
11. Positivity in itself to Coronavirus is not an indication for a cesarean section which in these patients should only be performed based on other obstetric or medical indications<sup>(33)</sup>.
12. In COVID-19 pregnant women, it is useful to be very cautious in inducing maturity of the lung by means of corticosteroids, since these drugs seem to worsen the course of the infection. If possible, evaluate each case with a neonatologist.



# 8.

## RECOMMENDATIONS FOR PEDIATRIC PATIENTS

Keep in mind that:

1. to date there is a paucity of information regarding COVID-19 in children;
2. children and infants are affected and with milder forms (X-ray more often negative; CT more sensitive) <sup>(34, 35)</sup>;
3. Lymphopenia is much less frequent in children (3%) <sup>(76)</sup>;
4. A small series of children with Covid-19 has shown a greater prevalence of peripheral halo (halo-sign) lung consolidations on CT <sup>(35)</sup>;
5. the criteria for the definition of Acute Respiratory Distress Syndrome (ARDS) and septic shock, the guidelines for the management of sepsis and septic shock and the use of non-invasive ventilation in children are different from those of adults <sup>(2)</sup>;
6. children desaturate more easily during intubation, therefore it is important to pre-oxygenate with 100% O<sub>2</sub> with a mask with a reservoir before intubating <sup>(2)</sup>;
7. a rectal swab may be useful in children to determine the timing of the termination of quarantine.

*Some authors have used the cycle threshold values of the serial rectal and nasopharyngeal swab tests to indicate viral load. Interestingly, the measurements have indicated that viral shedding from the gastrointestinal system could be greater and last longer than the respiratory tract <sup>(36, 37)</sup>.*

# 9.

## RECOMMENDATIONS FOR ONCOLOGIC AND IMMUNO- SUPPRESSED PATIENTS

1. Do not indiscriminately discontinue antineoplastic or immunosuppressive therapies <sup>(39-41)</sup>.
2. In cancer patients, consider the possibility of postponing the treatment cycle on a case-by-case basis <sup>(39)</sup>.
3. Immunosuppressant withdrawal is indicated if symptoms suggestive of infection appear <sup>(40)</sup>; in this case it is good practice to inform the physician responsible for the treatment promptly.
4. Steroids can be continued, but with caution <sup>(40)</sup>.
5. New immunosuppressant prescriptions or dose increases are not recommended during an epidemic <sup>(41)</sup>.
6. Consider the switch from parenteral drugs to others that can be administered at home (e.g. subcutaneously) to reduce access to outpatient clinics <sup>(40)</sup>.
7. Ensure non-deferred outpatient visits and postpone visits for long-term follow-up, after remote evaluation (telephone, email, etc.) <sup>(39, 40)</sup>.
8. Do not allow visitors in therapy rooms and allow the presence of a maximum of one visitor per patient in hospital stays <sup>(39)</sup>.

Please refer also to General Recommendations (section 1) for other indications relating to outpatients clinics.

# 10.

## RECOMMENDATIONS FOR HAEMODIALYSIS

(80)

As for other non postponable clinics, beyond the provision of separate entrance, room and staff for COVID-19 positive, suspected or under investigation patients and the respect of indications for the outpatient setting, reported in the General Recommendations and in the Recommendations for oncologic and immunosuppressed patients, it is recommended:

1. Screen patients through a structured interview on symptoms and contacts and measure body temperature, before entering the hemodialysis room.
2. Encourage patients to use their own transportation means.
3. To avoid waiting room crowding, let patients wait in their cars, recommend not to arrive beforehand.
4. If patients are forced to use medical transport, eliminate multiple transports and always organize single transports; sanitize the vehicles after the transport of affected or suspect patients.
5. Ask patient not to go the clinic, but notify by phone, in case of symptoms or close contacts with affected. Then consider postponing hemodialysis upon swab test results and address patient to local clinical pathway for COVID-19 diagnosis and treatment. There could be 2 scenarios: confirmed COVID-19 >> hemodialysis in the room for affected patients; COVID-19 not excluded >> hemodialysis in the room for suspected ones.
6. Prefer hemodialysis at home for all new entry patients.
7. Avoid that patients suspend treatment on the basis of being afraid of in-hospital contamination risk.
8. In case of Covid-19, pay attention to any dose adjustments required for medications used in the treatment of infection in patients with reduced kidney function.
9. Evaluate Covid-19 screening of hemodialysis patients and healthcare operators at the beginning of the epidemic and periodically, based on the local epidemiological situation, given the constant contact of these patients with the health services.

# 11.

## RECOMMENDATIONS FOR HOSPITAL DISCHARGE

1. The patient with fever without respiratory failure (normal EGA and walking test) and normal chest x-ray, <70 years and without risk factors (lung disease, diabetes mellitus and / or heart disease) can be discharged from the emergency room <sup>(14, 20)</sup> with indication of home isolation, waiting to run the swab sampling or its result.

### THE DISCHARGE PHYSICIAN

- obtains a telephone number to contact the patient for swab sampling and / or to communicate the result;
- provides information on how to access the pad (where and when).

If the swab test does not take place in the emergency department, but is performed elsewhere to another area or hospital, it is strictly suggested to use systems to avoid the loss of information.

The facility / service running the buffer must report the result as soon as it is available to the patient and, if positive, to the Public Health Department for establishing active surveillance.

2. At the end of the hospitalisation, write clearly on the discharge letter:

### CLINICALLY CURED PATIENT

(patient with clinical symptoms resolution, but still positive for swab) <sup>(38)</sup> or

**CURED PATIENT** (patient

who, in addition to resolving the symptoms, is negative in two consecutive swabs, carried out at least 24 hours apart) <sup>(38)</sup>;

**CLINICALLY CURED PATIENT:** write clearly on the discharge letter the indication to be observed at the home quarantine until the swab is negative on two determinations after 24 hours and the execution methods of the control buffer.

Although there is no clear supported evidence, it is considered appropriate to suggest patient retesting no earlier than 7 days and, if negative, confirm the negativity after at least 24 hours <sup>(38)</sup>.

**DISABLED PATIENT,** roommate of patient with positive swab or whose result is not yet known:

- write clearly the indication of home isolation on the discharge letter (up to 14 days from contact with the infected person) and indication to call 112 if symptoms appear;
  - assure a telephone number to communicate buffer result;
  - Communicate swab results as soon as available to the patient and, if positive, to public health trusts, in order to establish active surveillance <sup>(38)</sup>.
3. Any patient destined for nursing home, rehabilitative, hospice, long-term or similar health facility or referred to integrated home care, should have a negative test before discharge.

# 12.

## PSYCHOLOGICAL SAFETY OF STAFF

(43,44)

1. Create a healthy work, ethos and environment during crises and also to have systems in place to deal with subsequent distress and disorder.
2. Organisations which have the foresight to prepare their staff to deal with trauma might consider using interventions such as PFA (Psychological First Aid is a humane, supportive response to a fellow human being who is suffering and who may need support).
3. Consider that factors negatively affecting the psychological well-being of staff are:
  - concerns over the contracting the illness;
  - concerns for safety of their family;
  - witnessing the death of colleagues;
  - isolation from family and colleagues;
  - sense of being underappreciated;
  - extended length of epidemic.
4. Reduce mental health stigma to be reduced. The best ways of reducing stigma were believed to be raising awareness of mental health issues and telling people that it's quite normal to feel that way and have those feelings.
5. Educate healthcare workers who are exposed to trauma about the effects of cumulative stress. The training should be delivered either online 'because they can do it at their own convenience' or via educational leaflets 'rather than finding the time to spend on a day course'.

*The education about psychological trauma may lead to better understanding, better recognition of symptoms in oneself and in others, less judgement, and therefore reduced stigma, and that positive relationships with others in the workplace can have a positive impact on psychology.*

6. Maintain teamwork and effective leadership while at the same time providing individuals the opportunity to provide input into the decisions that affect their lives.

*Staff often experience severe emotional stress during viral outbreaks. It is often the nursing staff who feels the greatest level of stress due to their constant contact with sick patients, who may not be improving despite the nursing staff's best efforts. Physicians usually cope somewhat better with this situation because they are in a position to make treatment decisions and are less directly involved in implementing patient care.*

7. Be receptive to suggestions from nursing staff and support personnel.

*Input is empowerment and provides a sense that these critical staff retain some control over their situation. If suggestions are not acted on, clear explanations as to why they were not should be provided and alternatives should be explored.*

8. Administration needs to be supportive of staff and not be seen as pedantic and overly controlling.

*In cases where staff and support personnel did not feel appreciated or listened to, there was a high degree of dissatisfaction and an increased occurrence of absenteeism and staff strikes, which further reduced personnel in an already-strained system.*

9. Take care of yourself and your loved ones.

# 12.

## PSYCHOLOGICAL SAFETY OF STAFF

(43,44)

Healthcare providers are not invulnerable to experiencing their own emotional distress during outbreaks, and this distress can be compounded by caring for sick and distressed patients.

10. Make sure your basic needs are met, including: eating, drinking, and sleeping; take a break when you need one; check in with loved ones; practice the strategies to reduce distress listed above; and monitor yourself for stress reactions too.
11. Make efforts to ensure that your office and/or organisation has a viable plan to monitor the course of the outbreak and take rapid and appropriate action if needed.



# 13.

## MENTAL WELLBEING OF PATIENTS (45, 46, 47)

1. Medical and mental health clinicians are likely to encounter patients who are experiencing various levels of emotional distress about the outbreak and its impact on them, their families, and their communities.

*We must consider that COVID-19 patients have long hospital stays and in the early stages they will experience the anguish of having an aggravation of the disease with the possibility of being intubated. Furthermore, the limited staff available will not be able to guarantee them continuous assistance and their relatives as well.*

2. Providers should acknowledge uncertainty about emerging diseases and help patients understand that there is often an emotional component to potential health concerns.
3. Providers should be cognisant that the symptoms might extend beyond classical mental health symptoms to include relational struggles, somatic, academic, or vocational issues.
4. Every person, including mental health providers, can either react in fear, anger, or despair and regress, or can choose resilience and play as an active part of the solution.

In addition, providers should consider the following recommendations for promoting patients' mental wellbeing during emerging infectious disease outbreaks:

**BE INFORMED:** obtain the latest information about the outbreak from credible public health resources

in order to provide accurate information to your patients.

**EDUCATE:** healthcare providers are on the front lines of medical intervention and in a position to influence patient behaviors for protecting individual, family, and public health. *Psycho-education is of utmost importance in the aftermath of disasters. Patient education plays a critical role in both containing the disease and mitigating emotional distress during outbreaks. Depending on the nature of the outbreak, this can range from education about basic hygiene such as hand-washing and cough etiquette to more complex medical recommendations for prevention, diagnosis, and treatment.*

5. Let patients know what you, your office, or your organisation is doing to reduce the risk of exposure
6. Correct misinformation.  
*In this age of social media, misinformation can spread quickly and easily, causing unnecessary alarm. If patients present you with inaccurate information related to the outbreak, correct their misconceptions and direct them to vetted public health resources.*
7. Limit media exposure.  
*The excess media exposure to coverage of stressful events can result in negative mental health outcomes. Use trusted media outlets to gather the information you need, then turn them off—and advise your patients to do the same.*
8. 8. Anticipate and counsel about stress reaction.  
*Emotional distress is a common mental condition in the context of uncertain and potentially life-threatening situations, such as COVID-19 epidemic. A good first step for mitigating your patients' stress is*



# 13.

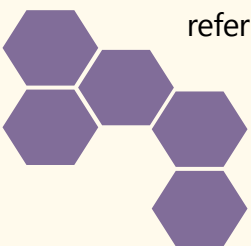
## MENTAL WELLBEING OF PATIENTS (45, 46, 47)

*to acknowledge that it exists and help normalise it (“I see that you’re stressed, and that’s understandable. Many people are feeling this way right now.”).*

9. Teach patients to recognise the signs of distress, including worry, fear, insomnia, difficulty concentrating, interpersonal problems, avoiding certain situations at work or in daily living, unexplained physical symptoms, and increased use of alcohol or tobacco.

*This will help them become more aware of the state of their mental health and head off distress before it becomes harder to manage.*

10. Discuss strategies to reduce distress, which can include:
  - being prepared (e.g., developing a personal/ family preparedness plan for the outbreak);
  - taking everyday preventive measures (e.g., frequent handwashing);
  - maintaining a healthy diet and exercise regimen;
  - talking to loved ones about worries and concerns;
  - engaging in hobbies and activities you enjoy to improve your mood;
  - if a patient is experiencing severe emotional distress or has a diagnosable mental illness, refer for specialized mental health care.



# 14.

## MORTUARY/ MORGUE OPERATING PROCEDURES

### MANAGEMENT OF THE DECEASED BODY WITH SUSPECT, PROBABLE OR CONFIRMED COVID-19 RESPIRATORY INFECTION

The proposed procedure is aimed at the safe management of the phases of acceptance, handling, custody, and discharge of the body with suspected, probable or confirmed diagnosis of COVID-19 <sup>(48)</sup>.

The objective has been pursued by drawing up the following recommendations:

1. the acceptance and handling of the body must be done by personnel equipped wearing the recommended PPE;
2. the body must be positioned on a sanitised metal stretcher for custody and subsequent investigations;
3. at the end of the investigations, the body must be placed in the coffin with the clothes and wrapped in a sheet soaked in disinfectant solution;
4. if the corpse is required to remain in the mortuary is necessary, pending or at the conclusion of the investigations, the same must take place inside a special closed body bag and dedicated refrigerated room;
5. at the end of the handling and transport operations, all the equipment used must be subjected to sanitisation.

### RECOMMENDATIONS FOR AUTOPSY INVESTIGATION IN CASES OF SUSPECT, PROBABLE OR CONFIRMED COVID-19.

1. For the safe and effective performance of HG3 (Hazard Group 3) autopsy investigations, is required:
  - generic risk assessment and adoption of universal standard precautions;
  - knowledge of possible pathological findings that can be highlighted;
  - the definition of SOP (Standard Operating Procedures) for the management of autopsies with high biological risk.
2. The use of universal precautions effectively protects against most risks related to SARS-CoV-2 infection. Professionals have a duty to carry out risk assessment for each case in order to prevent actions that could put operators at risk <sup>(49)</sup>;
3. at the end of the autopsy investigations, the body must be positioned in a body bag and transported in a refrigerated room;
4. disinfect the outside of the body bag with a hospital disinfectant applied according to the manufacturer's recommendations. It is also recommended in this phase the use of suitable PPE by each operator involved in the movement and exit phases of the body.

In addition, following an autopsy on a subject with suspect or confirmed COVID-19, the following

# 14.

## MORTUARY/ MORGUE OPERATING PROCEDURES

### RECOMMENDATIONS FOR DISINFECTION OF AUTOPSY ROOMS

should be applied:

1. keep ventilation systems active during cleaning;
2. wear disposable gloves when cleaning and handling cleaning or disinfectant solutions;
3. dispose of gloves after cleaning; do not wash or reuse the gloves in any case;
4. use eye protection, such as a visor or goggles, if splashing is expected;
5. if necessary, use respiratory protection based on the type of detergent or disinfectant;
6. wear a long-sleeved waterproof device to protect skin and clothing;
7. use disinfectants with indications of efficacy against human coronaviruses;
8. clean the surfaces and apply the disinfectant ensuring an adequate contact time for effective disinfection;
9. comply with the safety precautions and warnings indicated on the product label (for example, allow adequate ventilation in restricted areas and ensure correct disposal of the unused product or used containers);
10. avoid product application methods that cause the production of splashes or aerosols.

### ENVIRONMENTAL DISINFECTION

the available evidence has shown that coronaviruses are effectively inactivated by adequate sanitisation procedures that include the use of common hospital disinfectants, such as sodium hypochlorite (0.1% -0.5%), ethanol (62- 71%) or hydrogen peroxide (0.5%). There is currently no evidence to support a greater environmental survival or a lower sensitivity of SARS-CoV-2 to the aforementioned disinfectants <sup>(50)</sup>.

1. Hard and non-porous surfaces can be cleaned and disinfected as previously described.
2. Handle with gloves and disinfect properly after use, equipment such as cameras, telephones and keyboards, as well as all objects that remain in the autopsy room.
3. Cleaning activities must be supervised and periodically checked to ensure that correct procedures are followed. Sanitation personnel must be properly trained and equipped with suitable PPE.
4. After cleaning and removing the PPE, wash the hands immediately. Avoid touching the face with gloved or unwashed hands.
5. Environmental disinfection must include cleaning with water and detergent soap on all vertical and horizontal surfaces, followed by disinfection with hospital disinfectants effective against SARS-CoV-2.
6. For environmental decontamination, it is

# 14.

## MORTUARY/ MORGUE OPERATING PROCEDURES

necessary to use dedicated or disposable equipment. Reusable equipment must be decontaminated after use with a chlorine-based disinfectant. The use of special trolleys is strongly recommended, different from those used for cleaning common areas.

7. The instruments used for autopsies should be autoclaved or treated through chemical sterilisers.

# 15.

## RECOMMENDATIONS FOR HOSPITAL AND RESIDENTIAL PSYCHIATRIC FACILITIES (51,52)

1. Team organization and immediate isolation of the structure
  - Assigning specific responsibilities to clinical and management figures and designating a contact person for COVID-19, in constant contact with the local emergency team.
  - Closure of Outpatient Clinics and Day or Semi-residential Centers.
  - Cancellation of visits by relatives, friends and consultants.
  - Possible return of less serious patients to the families until the end of the emergency, illustrating the infection prevention measures.
2. Infectious risk containment actions
  - Provision of surgical masks, measurement of body temperature, assessment of Covid-19 related symptoms and contacts and hand-washing for any healthcare worker (HCW), before entering the facility. If history of close contact with positive COVID-19 and/or even mild symptoms should not be accepted within the facility.
  - HCWs should always be assigned to the same department and to the same section during the emergency
  - Monitoring of patients clinical condition should be carried out at least twice a day.
    - Rehabilitation activities must be reformulated on a “visible” social distancing, since the use of masks is not conceivable nor hands washing is practicable.
3. Actions aimed at protecting HCWs
  - In residential facilities rehabilitation activities should be carried out mainly outside.
  - Identify an isolation zone to be reserved for suspicious cases, pending diagnostic confirmation (COVID-19 area). The COVID-19 area should be set up in an area completely detached from the rest of the department, possibly with an independent entrance. It must be sanitized at least 2 times a day, keeping it always ready, even in the absence of cases to be isolated.
  - Swabs should be performed immediately on any suspicious case and his/her contacts.
  - Immediate isolation of positive patient and close contacts.
  - The clinical management of the COVID-19 require a multidisciplinary medical team including infectious disease specialist, anesthesiologist, internist and psychiatrist.
  - Beware of the numerous therapeutic interactions of psychotropic drugs.
3. Actions aimed at protecting HCWs
  - Arrange beds and bathrooms with shower, available exclusively to operators
  - Identify the Operators who may be available to remain in the isolation area for at least 15 days, in case of a positive

# 15.

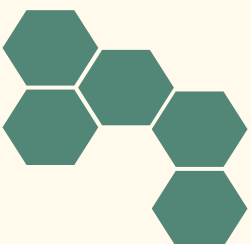
## RECOMMENDATIONS FOR HOSPITAL AND RESIDENTIAL PSYCHIATRIC FACILITIES (51,52)

COVID-19 patient case.

- Provide HCWs with the necessary PPE in case of suspected or confirmed COVID-19 patient.
- Teach them about PPE donning/doffing
- Set up a decontamination space outside the COVID-19 area to be used as a by personnel who should go into the COVID-19 area for an emergency.

#### 4. Communication

- Organize video calls between patients and family members or send them short videos.
- Organize video conferences to replace team meetings.



# 16.

## RECOMMENDATIONS FOR LONG-TERM FACILITIES AND NURSING HOME

(53, 54)

### GENERAL ACTIONS

1. External access only allowed to facility operators; social and health services, general practitioners and support administrators, if necessary.
2. Unloading of goods in the external area and collection by personnel equipped with PPE
3. Limit, as far as possible, hospitalization for specialist visits and instrumental examinations.
  - not necessary (hospital);
  - in case of a network of residences, identify an entire facility dedicated to COVID-19 with a “filter” and “isolation” area.
2. Limit visits by GPs or specialists and individual physiotherapy activities to those considered absolutely necessary and non-deferrable.
3. Suspend group activities and the sharing of common spaces within the structure.

For other indications see also Recommendations for hospital and residential psychiatric facilities (points 1- 2).

### SPECIFIC ACTIONS

1. Organization of two functional areas, possibly with single rooms and dedicated staff:
  - a “filter” area for the reception of new guests, equipped with a doctor’s certificate of absence of symptoms/ suspect contacts and/or negative swab or guests returned from the hospital with diagnosis other than COVID-19 and negative swab before discharge;
  - “isolation” area inside the residence where to host suspect cases awaiting diagnostic confirmation, guests who have returned from the hospital who have only been cured clinically (swab still positive) or to treat confirmed cases, if highly specialized care is

For other indications see also Recommendations for hospital and residential psychiatric facilities (points 3-4).

# 17.

## RECOMMENDATIONS FOR GENERAL PRACTITIONERS

### INFECTION PREVENTION AND CONTROL AND OFFICE ORGANIZATION

- Prepare organizational procedures to limit attendance (e.g. visits by appointment) and regulate access through standardized telephone triage <sup>(55)</sup>, aimed at stratifying the risk of COVID-19 and the urgency of other problems.
- Prevent people with fever and / or respiratory syndromes arrive to the office.
- Provide a maximum number of people per area (m<sup>2</sup>) and per hour, so that no more than 2-3 people are simultaneously in the waiting room at a minimum distance of 2 meters and for more than 15 minutes <sup>(8)</sup>.
- Favor and implement the electronic transmission of prescriptions.
- Make available and mandatory the use of personal protective equipment, (PPE) the disinfection of hands and shoes, body temperature measurement on entrance (termoscanner) for patients <sup>(63)</sup>.
- Arrange for proper disposal at the end of each visit of the disposable material of patients and staff, according to the procedures for special biohazardous waste, in closed disposable bags sprinkled with disinfectant and stored in special rooms
  - Prepare sanitization and ventilation procedures: sanitize the medical room (surfaces, used equipment, examination table) after each visit and at the

end of each day with solutions based on 0.5% sodium hypochlorite or ethyl alcohol solution at 70% <sup>(8)</sup>.

- Provide administration staff with PPE and proper training (FAD, video tutorial, poster, etc.).
- Upon arrival in the office, the physician must wear special washable uniforms (at least 2 available), working closed shoes and wear PPE (FFP2, disposable goggles and gloves for non-suspicious cases; FFP3, disposable gown, disposable waterproof full suit, headset, glasses, visor, cover shoes and 2 pairs of gloves for visits of suspicious cases). Disposable devices must be changed on each visit.

### AT THE DISTRICT LEVEL

- Establishment of special continuity of care units that support general practitioners in home management (swabs, laboratory tests, home surveillance).

*Early identification and treatment at home are useful to reduce the congestion of hospitals and intensive care in particular, as they would be associated with a lesser evolution of the disease.*

### IDENTIFICATION AND MANAGEMENT OF SUSPECTED OR CONFIRMED CASES <sup>(63)</sup>

- Have triage cards based on checklists - better if computerized - that include items for the identification of suspected cases, for the stratification of severity <sup>(56)</sup>, the choice of the appropriate setting and appropriate



# 17.

## RECOMMENDATIONS FOR GENERAL PRACTITIONERS

treatment, the mandatory reports according to national and local provisions (to the Public Health units and special continuity units, in case of home management).

- Keep active contact with COVID-19 patients by telephone or through other communication tools (e-mail, whatsapp, telemedicine) for clinical-prognostic reassessment, at different intervals depending on the clinical severity. Ensure h24 availability when needed (in case of onset or worsening of symptoms), including holidays and pre-holidays.
- Inform - also by written instructions or video tutorials sent by email - all the patient on how to prevent contagion, disinfection measures (places and hands), respiratory etiquette, social distancing and the behavioral rules for home isolation.
- Off-label therapies must be prescribed after checking contraindications and/or interactions with other drugs taken by the patient and after informed consent signed by the patient.

### COMMUNICATION

- The information flow must be constant, computerized and traceable, possibly using electronic media and telemedicine and teleconsultation systems <sup>(57)</sup>.
  - The reporting of suspicious and/or symptomatic cases to special units of care continuity for diagnostic confirmation and home care must be carried out in a traceable

and timely way through any available communication channel (i.e. whatsapp, email, portal, app, etc.).

- The swabs and/or serological tests results must be returned to the GP in a traceable way to be recorded in the electronic medical record.
- The special units of care continuity, the GPs and the hospital must use any available tool to efficiently communicate each other (app, WUP, mobile phones, emails, shared software, teleconsultation) in a constant and continuous way by sharing any information about patient's journey (tests results, clinical picture, any ongoing therapy, clinical monitoring, hospital admissions and discharge) as an integrated multi professional team.
- Keep active contacts with all the assisted people through information campaigns on regional and national communications, healthcare company and organizational regulations of the office, hygiene and behavioral rules, PPE, along with psychological and moral support through all available communication systems (whatsapp, e-mail, phone).
- Carry out periodically (at least once a month) a pro-active phone call aimed at the assessment of the most fragile patients (elderly, disabled, chronic patients).

### OUTCOME MEASURES FOR GENERAL PRACTITIONERS

1. Hospitalization rate for COVID-19.

# 17.

## RECOMMENDATIONS FOR GENERAL PRACTITIONERS

2. Mortality of hospitalized patients for COVID-19.
3. Hospitalization rate for chronic non-covid diseases.
4. Number of COVID-19 cases stratified by age
5. Number of COVID-19 cases with STEMI/NSTEMI.
6. Number of COVID-19 cases with COPD.
7. Number of COVID-19 cases with diabetes.
8. Number of COVID-19 cases with multiple pathologies or social assistance frailties.
9. Infection rate in the assisted population

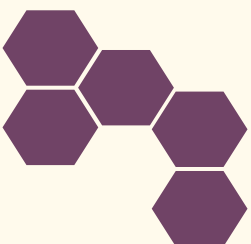
### PROCESS MEASURES FOR GENERAL PRACTITIONERS

1. Number of triage forms filled in
2. Number of cases reported to the local Public Health unit.
3. Percentage of activations of special units of care continuity.
4. Number of drug prescriptions ( COVID-19 therapeutic protocol).
5. Percentage of patients with co-morbidities
6. Percentage of health personnel equipped and not equipped with suitable PPE.
7. Number of untreated patients in adequate level of care.
8. Percentage of personnel trained for emergency management.

# 18.

## RECOMMENDATION FOR HOME ISOLATION (38)

1. Provide prevention measures and explain them to patients in home isolation also by using designs, charts or pictures.
2. Give also clear indications on alarm symptoms: promote information diffusion of telephone numbers to call in case of their occurrence.
3. Provide call centers, online chats, FAQs and video tutorials to consult in case of doubts.



# 19.

## RECOMMENDATIONS FOR PERSONS IN QUARANTINE

(42)

1. Information represents the key success factor; quarantined persons must be constantly informed and updated on the epidemic progress.
2. It is necessary to provide food and other materials and any necessary drugs without making people feel abandoned or alone.
3. The quarantine period should be short and the duration should not be modified except in extreme circumstances.
4. Most of the side effects derive from the freedom restriction imposition; voluntary quarantine is associated with less stress and fewer long-term complications, therefore it is necessary to explain clearly the reasons for such suggested behaviours.
5. Public health officials should stress the selfless choice of self-isolation.

Quarantined healthcare workers can be helpful in producing useful documents or other materials while at home for their colleagues. They could contribute by making suggestions and stay in touch with social media.



# 20.

## MEASUREMENT (58, 59, 60)

It is important that we measure the impact of our actions. We include some measures that may be of use.

### OUTCOME MEASURES

Outcome measures should be collected in order to support the monitoring of effective provider (hospital) epidemic/pandemic response including the capacity to adequately treat patients with other common severe conditions like heart attacks, strokes, trauma, copd in order to assure that the health of the public is protected to the fullest extent possible.

1. Hospitalisation rate for COVID-19 (indirect outcome measure of the territory).
2. In-hospital Mortality rate of patients hospitalized for COVID-19.
3. Average Length of Stay of COVID-19 patients.
4. Percentage of COVID-19 patients admitted to ICU.
5. In-hospital mortality rate of NO-COVID-19 patients hospitalised for AMI.
6. In-hospital mortality rate of NO-COVID-19 patients hospitalized for Stroke.
7. In-hospital mortality rate of NO-COVID-19 patients hospitalized for COPD.
8. Percentage of NO-COVID-19 hospitalized patients that acquired COVID during the hospitalisation.
9. COVID-19 infection rate among staff.

10. Survival rates.

Where possible indicators 1-7 should be stratified by age groups.

Additionally, the proposed outcome measures should be used and interpreted with great caution if used to benchmarking care quality between providers. In this case, consistent data definitions should be adopted and measures from 1 to 7 should be adjusted for potential confounding factors (i.e. patient case mix) in order to draw meaningful and correct comparisons among providers.

### PROCESS MEASURES (SOME EXAMPLES)

1. Length of Stay.
2. Average length of stay in ICU of infected.
3. Average length of stay in hospital.
4. Percentage of infected admitted to ICU.
5. Percentage of people with comorbidities
6. Profiles
  - Age
  - Gender
  - Ethnicity
  - Comorbidity
7. Percentage of staff with and without correct equipment.
8. Number of patients not treated in appropriate level of care.
9. Percentage staff trained.
10. Number of tests performed to hospital staff.

# 20.

## MISURAZIONE DEGLI OUTCOME (58, 59, 60)

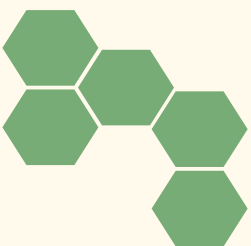
### **BALANCING MEASURES**

1. Staff infection rate.
2. Staff mortality rate.
3. Staff well being.
4. Illness and sickness rates.
5. Mental illness.



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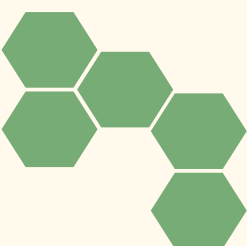
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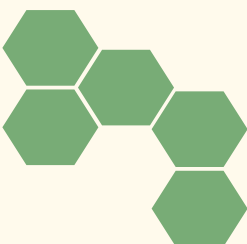
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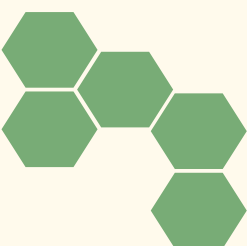
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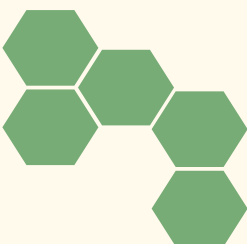
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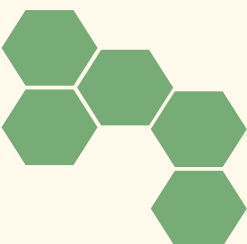
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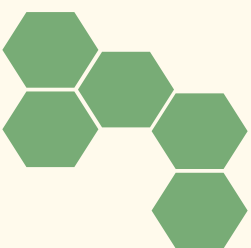
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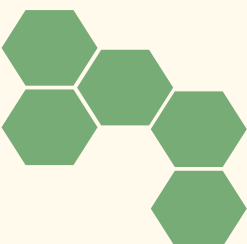
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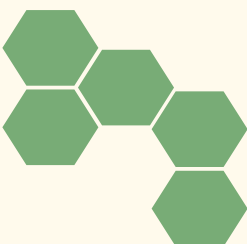
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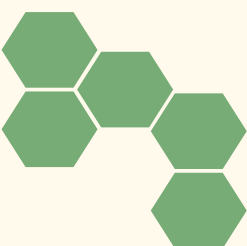
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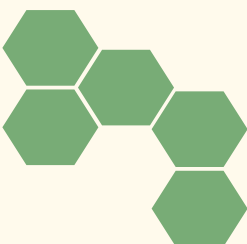
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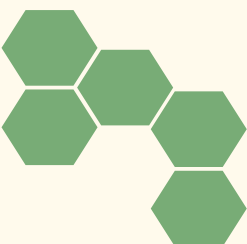


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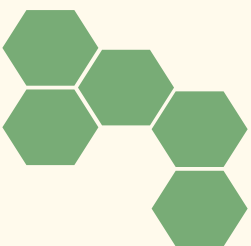


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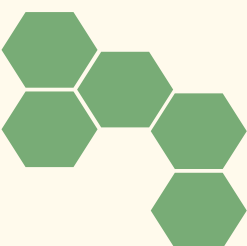
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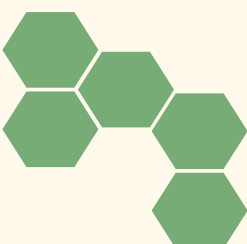
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# APPENDIX: MEDICATIONS

**TABLE 1 - CHLOROQUINE AND HYDROXY-CHLOROQUINE: MAIN DRUG INTERACTIONS**

DRUGS	INTERACTIONS
CHLOROQUINE	<p>Antacids based on aluminum, calcium and magnesium and kaolin can reduce their absorption</p> <p><b>In association with:</b></p> <ul style="list-style-type: none"><li>• Corticosteroids accentuation of any myopathies or cardiomyopathies</li><li>• Phenylbutazone can induce exfoliative dermatitis</li><li>• Isoniazid, Amiodarone, Carbamazepine, Phenytoin, Phenothiazide, Ketoconazole and MAO inhibitors (Mono-Amino-Oxidase Inhibitors) risk of hepatotoxicity</li><li>• Mefloquine and bupropion risk of convulsions</li><li>• Metronidazole possible dystonic reactions</li><li>• Penicillamine serious haematological or renal adverse events</li><li>• Pyrimetamine / sulfadoxineskin reactions</li></ul> <p><b>Effects of chloroquine on other drugs</b></p> <ul style="list-style-type: none"><li>• Ampicillin reduced absorption (administer at least 2 hours after chloroquine)</li><li>• Class IA and III antiarrhythmics, Tricyclic antidepressants, Antipsychotics increased risk of ventricular arrhythmia</li><li>• Antiepileptic antagonism on anticonvulsant effects</li><li>• Cyclosporine increase in plasma concentration</li><li>• Digoxin increase in plasma concentration and relative toxicity</li><li>• Methotrexate potentiation of the action</li><li>• Neostigmine and Pyridostigmine antagonism of the effects</li><li>• Vaccines antibody response reduction ONLY with rabies vaccine</li></ul>



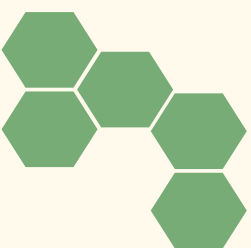
**H Y D R O X Y -  
CHLOROQUINE**

**In association with:**

- Phenylbutazone can induce exfoliative dermatitis
- Isoniazid, Amiodarone, Carbamazepine, Phenytoin, Phenothiazide, Ketoconazole and MAO MAO inhibitors (Mono-Amino-Oxidase Inhibitors) can cause hepatotoxicity

**Effects of hydroxychloroquine on other drugs**

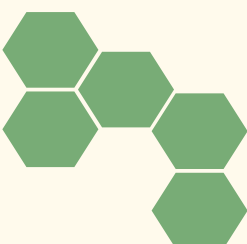
- Antiepileptics antagonism on anticonvulsant effects
- Cyclosporine increased plasma concentrations
- Digoxin increased plasma concentration and relative toxicity
- Insulin and Antidiabetics potentiation of hypoglycemic effects



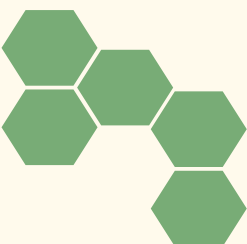
# APPENDIX: MEDICATIONS

**TABLE 2 - LOPINAVIR/RITONAVIR: MAIN INTERACTIONS AND RECOMMENDATIONS**

COADMINISTERED DRUG	MECHANISM OF INTERACTION	CLINICAL RECOMMENDATIONS
RETROVIRAL AGENTS Nucleoside reverse transcriptase inhibitors (NRTIs), Non-nucleoside reverse transcriptase inhibitors (NNRTIs), HIV CCR5 - antagonist, Integrase inhibitor, Inhibitors of HIV protease		Specialist advice, dose adjustment is not required in most cases. Co-administration with other HIV protease inhibitors (PIs), according to current guidelines, is not recommended.
<b>Antacids</b> No contraindications		
<b>Alpha antagonists</b>		
ALFUZOSIN	Increased concentration (CYP3A inhibition)	Contraindicated (hypotension)
<b>Analgesic Drugs</b>		
FENTANYL	Increased concentration (CYP3A inhibition)	Close monitoring (risk of respiratory)
<b>Antianginal Drugs</b>		
RANOLAZINE	Increased concentration (CYP3A inhibition)	Contraindicated
<b>Antiarrhythmics</b>		
AMIODARONE, DRONEDARONE	Increased concentration (CYP3A inhibition)	Contraindicated (arrhythmia)
DIGOXIN	Increased concentration (P-gp inhibition)	Plasma level monitoring
BEPRIDIL, SYSTEMIC LIDOCAINE, QUINIDINE	Increased concentration	Plasma level monitoring



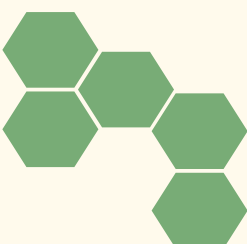
<b>Antibiotics</b>		
CLARITHROMYCIN	Moderate increase of under-curve area (CYP3A inhibition)	Dose reduction in kidney failure (CrCL < 30 ml/min); attention in patients with impaired liver and kidney function
<b>Antineoplastics Specialist Advice</b>		
<b>Anticoagulants</b>		
WARFARIN	CYP2C9 induction	INR monitoring
RIVAROXABAN	AUC: ↑ 153%, Cmax: ↑ 55% (CYP3A and P-gp inhibition)	Contraindicated (bleeding)
VORAPAXAR	Increased concentration (CYP3A inhibition)	Contraindicated
<b>Antiepileptic</b>		
PHENYTOIN	Concentrazioni diminuite (induzione del CYP2C9 e del CYP2C19)	Plasma level monitoring
CARBAMAZEPINE, PHENOBARBITAL	Increased Carbamazepine concentration (CYP3A inhibition); reduced Lopinavir concentration (CYP3A induction)	Plasma level monitoring
<b>Antidepressants and anxiolytics</b>		
TRAZODONE	AUC: ↑ 2,4-times	Dose reduction
<b>Antifungals</b>		
KETOCONAZOLE	Increased concentration (CYP3A inhibition)	Dose reduction



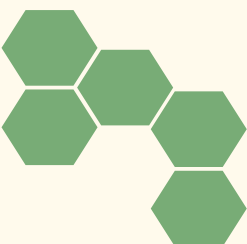


# APPENDIX: MEDICATIONS

<b>Antigout</b>		
COLCHICINE	AUC: ↑ 3-volte; Cmax: ↑ 1,8-times (CYP3A and/or P-gp inhibition)	Contraindicated
<b>Anti Infectives</b>		
ASTEMIZOLE, TERFENADINE	Increased concentration (CYP3A inhibition)	Contraindicated (severe arrhythmias)
<b>Antinfettivi</b>		
FUSIDIC ACID	Increased concentration (CYP3A inhibition)	Contraindicated (rhab- domyolysis)
<b>Antimycobacterial agents</b> Specialist Advice		
<b>Benzodiazepines</b>		
MIDAZOLAM	Oral administration: AUC: ↑ 13-times Parenteral administration: AUC: ↑ 4-times (CYP3A inhibition)	Oral administration con- traindicated; close moni- toring for parenteral admini- stration
<b>Beta2 agonists</b>		
SALMETEROL	Increased concentration (CYP3A inhibition)	Contraindicated (severe cardiovascular event and arrhythmias)
<b>Calcium Channel Blockers</b>		
FELODIPINE, NIFEDIPINE, NICARDIPINE		

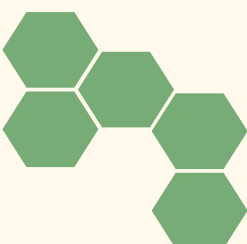


<b>Steroids</b>		
DEXAMETHASONE	Reduction of Lopinavir concentrations (CYP3A induction)	Clinical monitoring of anti-viral activity
<b>Phosphodiesterase inhibitors</b>		
AVANAFIL, SILDENAFIL	Increased concentration (CYP3A inhibition)	Contraindicated
<b>Ergot Alkaloids</b>		
DIHYDROERGOTAMINE AND OTHERS	Increased concentration (CYP3A inhibition)	Contraindicated
<b>Intestinal Prokinetics</b>		
CISAPRIDE	Increased concentration (CYP3A inhibition)	Contraindicated
<b>Direct anti-HCV agents</b>	Increased plasma concentration (combined mechanisms)	Contraindicated
<b>HCV protease inhibitors</b> Contraindicated		
<b>Immunosuppressors</b>		
CICLOSPORINE	Increased concentration (CYP3A inhibition)	Plasma level monitoring
<b>Statins</b> Contraindicated; fluvastatin and pravastatin tolerated		
<b>Opioids</b>		
METHADONE	Decrease in concentration	Plasma level monitoring



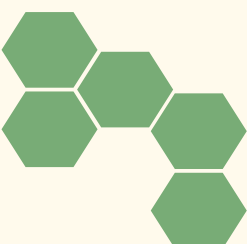
# APPENDIX: MEDICATIONS

<b>Contraceptives</b>		
Ethinylestradiol	Decrease in concentration	Use additional contraceptive methods
<b>Hormone Replacement Therapy (HRT)</b>		
Levothyroxine	Potential interactions not well documented	TSH monitoring during the first month from the beginning and / or from the end of the treatment



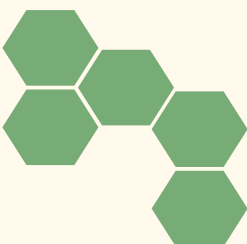
**TABLE 3 - DARUNAVIR/COBICISTAT: MAIN INTERACTIONS AND RECOMMENDATIONS**

COADMINISTERED DRUG	MECHANISM OF INTERACTION	CLINICAL RECOMMENDATIONS
<b>Anti-retroviral agents (HIV)</b>		
Inhibitors of the strand transfer of ' integrase , inhibitors nucleoside / nucleotide HIV reverse transcriptase inhibitors (NRTIs)		Specialist advice, no dose adjustment necessary, except for Emtricitabine / tenofovir alafenamide
Non- nucleoside / nucleotide inhibitors of HIV reverse transcriptase (NNRTI)		Specialist advice, non-recommended co-administration RILPIVIRINE, the increase of which is not considered relevant, is an exception
<b>CCR5 A ntagonists</b>		
MARAVIROC	Increased concentration (CYP3A inhibition)	Specialist advice for dose adjustment
<b>Al / M or calcium carbonate based antacids</b>		
		No dose adjustment
<b>Alpha antagonists</b>		
ALFUZOSIN	Increased concentration (CYP3A inhibition)	Contraindicated (hypotension)

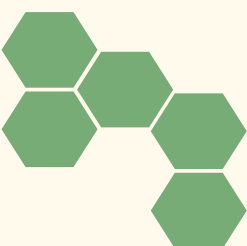


## APPENDIX: MEDICATIONS

<b>An aesthetic</b>		
AL FENTANYL	Increased concentration (inhibition of CYP3A4)	Dose reduction and monitoring (respiratory depression risk)
<b>Antianginal / tymph antiaries</b>		
AMIODARONE, DRONEDARONE, CHINIDINA, BEPRIDILE, IVRABRADINA, RANOLAZINA	Increased concentration (inhibition of CYP3A and/or CYP2D6)	Contraindicated
DYSOPYRAMID, FLECAINIDE, SYSTEMIC LIDOCAINE, MEXILETINE, PROPAPHENONE	Increased concentration (inhibition of CYP3A and/or CYP2D6)	Caution and monitoring
DIGOXIN	Increased concentration (P-glycoprotein inhibition)	Dose titration and accurate monitoring of drug concentration
<b>Antibiotics</b>		
Clarithromycin	Increased AUC (CYP3A inhibition)	Caution and dose adjustment in patients with renal impairment (CrCL <30 ml / min)
<b>Anticoagulants</b>		
WARF ARIN	Theoretical mechanism of alteration of plasma concentrations	INR monitoring
APIXABAN, EDOXABAN, RIVAROXABAN	Increased plasma concentrations (inhibition of CYP3A and P-gp)	Contraindicated

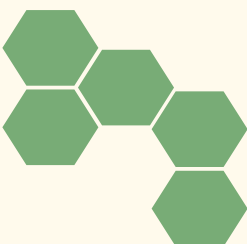


DAPIGATRAN; TICAGRELOR	Increased plasma concentrations (inhibition of CYP3A and P-gp )	Contraindicated
<b>Anticonvulsants</b>		
CLONAZEPAM	Increased concentration (CYP3A inhibition)	Clinical monitoring
CARBAMAZEPINA, FENOBARBITALE, FENITOINA	Reduced concentrations of darunavir and/or cobicistat (CYP3A induction)	Contraindicated
<b>Antidepressants and anxiolytics</b>		
ST. JOHN'S GRASS	Reduction of darunavir and / or cobicistat concentrations (CYP3A induction).	Contraindicated
PAROXETINE, SERTRALINA, AMITRIPTILINA, DESIPRAMINA, IMIPRAMINA, NORTRIPTILINA, TRAZODONE	Increased plasma concentrations (CYP2D6 and/or inhibition CYP3A)	Dosage reduction and clinical monitoring
<b>Antidiabetic</b>		
METFORMIN	Increased plasma concentration	Dosage reduction and clinical monitoring
<b>Antidiabetic</b>		
DOMPERIDONE	Not studied	Contraindicated

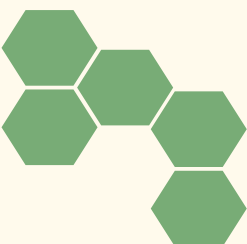


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<b>Antifungals</b>		
CLOTRIMAZOLO, FLUCONAZOLO, ITRACONAZOLO, ISAVUCONAZOLO, POSACONAZOLO	Increased concentration (inhibition of CYP3A and / or P-gp)	Caution, clinical monitoring and dosing Voriconazole contraindicated
<b>Antigout</b>		
COLCHICINE	Increased concentration (inhibition of P- gp and/or CYP3A4)	Dosage reduction, contraindicated in the presence of hepatic or renal impairment
<b>H2 receptor antagonists</b>		
No dose adjustment necessary		
<b>Antimycobacterials</b>		
Specialized evaluation, tententially contraindicated		
<b>Antipsychotics / neuroleptics</b>		
PERFENAZINA, RISPERIDONE, TIORIDAZINA	Increased plasma con- centrations (inhibition of CYP3A, CYP2D6 and/or P- gp)	Dose reduction and clinical monitoring
LURASIDONE, PIMOZIDE, SERTINDOLO, QUETIAPINA		Contraindicated
<b>Anticancer</b>		
Theoretical mechanism of concentration increase (CYP3A inhibition)		
Specialist evaluation, extreme caution		
<b>Beta2 agonists</b>		
SALMETEROL	Increased concentration (CYP3A inhibition)	Contraindicated (serious cardiovascular adverse events, arrhythmias)



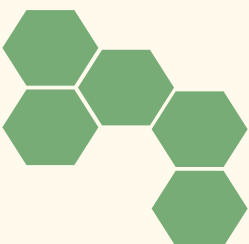
<b>Beta blockers</b>		
CARVEDILOL, METOPROLOL, TIMOLOL	Plasma concentrations increased (CYP3A inhibition)	Dose reduction and clinical monitoring
<b>Calcium antagonists</b>		
AMLODIPINA, DILTIAZEM, FELODIPINA, NIFEDIPINA, NICARDIPINA, VERAPAMIL	Increased concentration (inhibition of CYP3A and / or CYP2D6)	Dose reduction and clinical monitoring
<b>Corticosteroids</b>		
DEXAMETHASONE	Reduction of Darunavir and / or cobicistat concentrations (CYP3A induction)	Caution
<b>Proton pump inhibitors</b>		No dose adjustment
<b>Inhibitors of phosphodiesterase</b>		
TADALAFIL, SILDENAFIL	Increased concentration (CYP3A inhibition)	Contraindicated
<b>Antivirals direct action against HCV (inhibitors NS3-4A protease)</b>	Increased plasma concentrations (combination of mechanisms)	Contraindicated
<b>Endothelial receptor antagonists (Bosentan)</b>	Increased concentration (theoretical consideration)	Contraindicated
<b>Immunosuppressant</b>		
CYCLOSPORINE	Increased concentration (CYP3A inhibition)	Monitoring of drug levels
EVEROLIMUS		Contraindicated
<b>Narcotics, Opioids</b>		
METHADONE	Increased concentration (theoretical consideration)	Monitoring of drug levels





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BUPRENORPHINE / NALOXONE	Increased concentration (theoretical consideration)	Clinical monitoring
FENTANYL, OXYCODONE, TRAMADOL	Increased concentration (theoretical consideration)	Clinical monitoring
<b>Opioid antagonists</b>		
NALOXEGOL	Not studied	Contraindicated
<b>Sedatives / hypnotics</b>		
BUSPIRONE, CLORAZEPAM, DIAZEPAM, ESTAZOLAM, FLURAZEPAM, ZOLPIDEM	Increased concentration ( CYP3A inhibition)	Caution, dose reduction and clinical monitoring
MIDAZOLAM (PARENTERAL)		Only in intensive care.
MIDAZOLAM (ORAL)		Contraindicated
<b>Urological drugs</b>		
FESOTERODINA, SOLIFENACINA	Not and clever or	Caution, dose reduction and clinical monitoring
DAPOXETINE	Not and clever or	Contraindicated
<b>Contraceptives</b>		
ETHINYLESTRADIOL	Alteration of plasma con- centrations	Use additional methods of contraception
DROSPIRENONE		Monitoring for possible hypokalaemia
<b>Statins and other hypo-lipidemic agents (Lomitapide)</b>		
		Contraindicated



**TABLE 4 - ADVERSE EVENTS**

	<b>LOPINAVIR/ RITONAVIR</b>	<b>DARUNAVIR / COBICISTAT</b>	<b>CHLOROQUINE</b>	<b>HYDROXYCHLOROQUINE</b>	<b>TOLICIZUMAB</b>
Serious adverse effects	<ul style="list-style-type: none"> <li>• Hypersensitivity reaction, angioedema</li> <li>• Stevens-Johnson syndrome / Toxic epidermal necrolysis / Erythema multiforme</li> <li>• QT prolongation &amp; Torsade de Pointes</li> <li>• AV block, PR prolongation</li> <li>• Hyperglycemia, hypertriglyceridemia</li> <li>• Renal failure</li> <li>• Anemia, leukopenia, neutropenia</li> <li>• Pancreatitis</li> <li>• Hepatotoxicity</li> </ul>	<ul style="list-style-type: none"> <li>• Hepatotoxicity</li> <li>• Anorexia, hypercholesterolaemia, hypertriglyceridemia</li> <li>• Renal failure</li> <li>• Stevens-Johnson syndrome (rarely)</li> </ul>	<ul style="list-style-type: none"> <li>• QT prolongation &amp; Torsades de Pointes</li> <li>• Reduction in seizure threshold</li> <li>• Anaphylaxis or anaphylactoid reaction</li> <li>• Neuromuscular impairment</li> <li>• Neuropsychiatric disorders (potential to increase delirium)</li> <li>• Pancytopenia, neutropenia, thrombocytopenia, aplastic anemia</li> <li>• Hepatitis</li> </ul>	<ul style="list-style-type: none"> <li>• Hypoglycemia</li> <li>• QT prolongation</li> <li>• Cardiomyopathy</li> <li>• Muscle asthenia</li> <li>• Retinal or visual field alterations</li> <li>• Skin reactions</li> </ul>	<ul style="list-style-type: none"> <li>• Interstitial pneumonia</li> <li>• Infections</li> <li>• Leukopenia, neutropenia hypofibrinogenemia</li> <li>• Upper respiratory infections</li> <li>• Herpes simplex and zoster</li> <li>• Oral ulcerations</li> <li>• Complicated diverticulitis</li> <li>• Hepatotoxicity</li> </ul>
Common adverse reactions	<ul style="list-style-type: none"> <li>• Nausea / vomiting, diarrhea</li> <li>• Insomnia, anxiety</li> </ul>	<ul style="list-style-type: none"> <li>• Nausea / vomiting, diarrhea</li> <li>• Insomnia, anxiety</li> <li>• Headache</li> <li>• Rash</li> <li>• Muscle Pain</li> </ul>	<ul style="list-style-type: none"> <li>• Nausea / vomiting, diarrhea, abdominal pain</li> <li>• Visual disturbance, headache</li> <li>• Extrapyrasidal symptoms</li> </ul>	<ul style="list-style-type: none"> <li>• Nausea / vomiting, diarrhea, abdominal pain</li> <li>• Visual disturbance, headache</li> <li>• Skin rash, itching</li> <li>• Extrapyrasidal symptoms</li> </ul>	<ul style="list-style-type: none"> <li>• Hypertension</li> <li>• Headache</li> <li>• Skin reactions</li> <li>• Conjunctivitis</li> <li>• Hypercholesterolemia</li> <li>• Abdominal pain, gastritis</li> <li>• Cough, dyspnea</li> </ul>
Contra indicated in	<ul style="list-style-type: none"> <li>• Cardiac disease (ischemic heart disease, cardiomyopathy, structural heart disease, QT prolongation)</li> <li>• Liver disease</li> </ul>	<ul style="list-style-type: none"> <li>• Liver failure (class C Child- Pugh)</li> <li>• Haemophilia</li> </ul>	<ul style="list-style-type: none"> <li>• Porphyria</li> <li>• G6PD deficiency</li> <li>• Epilepsy</li> <li>• Heart failure</li> <li>• Recent myocardial infarction</li> </ul>	<ul style="list-style-type: none"> <li>• Porphyria</li> <li>• Retinopathy</li> <li>• Maculopathies</li> <li>• Children &lt;6a &lt;31 Kg</li> </ul>	<ul style="list-style-type: none"> <li>• Administration of alive or attenuated vaccines</li> </ul>
Monitoring	<ul style="list-style-type: none"> <li>• Transaminases</li> </ul>	<ul style="list-style-type: none"> <li>• Kidney function</li> </ul>	<ul style="list-style-type: none"> <li>• Serial complete blood count</li> <li>• QT interval</li> </ul>	<ul style="list-style-type: none"> <li>• EBlood count, glycemia,</li> <li>• QT interval</li> </ul>	<ul style="list-style-type: none"> <li>• Cholesterol, blood count, transaminases</li> </ul>

