



PATIENT SAFETY RECOMMENDATIONS FOR COVID-19 EPIDEMIC OUTBREAK

Lessons from the Italian Experience

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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 (1).

1. Assess the work system:
 - a. Team and organisational culture and communication
 - b. Environment
 - c. Tasks required and skills to complete tasks
 - d. Equipment for patient care and to protect staff
 - e. The people needed to provide care
 - f. The patients who will receive care
2. Develop reliable pathways of care.
3. Measure the outcomes of care.

ISQua is honoured to publish these recommendations with our partners in Italy.

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 FOR THE WORK SYSTEM

Building the Team including communication and team culture

1. Emergency taskforce 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 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 swabs, 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 the pandemic. Secondly, the reporting of Adverse Events should be encouraged in order to maintain the underpinning safety climate in order to prompt corrective and improvement actions. Consider quick reporting tools such as confidential IM or audio-messages (e.g. *WhatsApp, WeChat, Telegram, Line* etc.)
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 (2), 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 (3).

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 (4).
2. Contact and airborne precautions are recommended when performing aerosol generating procedures (AGPS), including intubation and bronchoscopy (4).
3. Prevent biosafety precautions shortage by extended use and limited re-use of full-face shields and disposable facial filtering masks (5), 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 (5).

The infection spreads so quickly that a depletion of reserve medical supplies is almost unavoidable.

Equipment needed to treat patients

1. Give suspected or confirmed patients a surgical mask to put on, at their first contact with healthcare services (6).
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
 - e. suction pumps.

are available and well-functioning (7).

Environment

1. Strictly apply, without exceptions, the indications for disinfection of environments and tools (sodium hypochlorite at 0.5% or 70% ethyl alcohol solution) (8). 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 (shortness of breath) 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.

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.

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. create separate unclean/clean paths, even with the help of external mobile structures (i.e. tents).
2. Contacts of positive patients must follow the instructions provided by those who carry out epidemiological investigation and be clinically evaluated in the locally designated sites, only if symptomatic.
 3. 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.)
 - a. If the criteria of case or suspicion are met, refer the patient for evaluation, according to local procedures.
 - b. General practitioners will provide their patients with useful information by social networks, email or other tools and keep them updated.

2. 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). Quality of RT-PCR testing is a crucial issue. Both pre-analytical and analytical variables should be carefully considered, and a validation process should be performed according to ISO 15189 (3 protocols). (9)

2. Many of the most common symptoms of novel coronavirus disease (COVID-19) are like 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.

Rhinorrhea ("runny nose") is not a symptom of COVID-19 and nasal congestion ("stuffy nose") is reported only by 4.8% of patients (10).

3. The most common COVID-19 symptoms are: fever (88%), dry-cough (68%), fatigue (38%), thick sputum production (34%), shortness of breath (19%), arthro-myalgia (15%), sore throat (14%), headache (13.6%), chills (11%), nausea/vomiting (5%), nasal congestion (4.8%), diarrhoea (3.7%).

Data from a series of 55,924 laboratory confirmed cases of COVID-19 in China in the period up to February 2020 (11).

4. Beware of patients with gastrointestinal symptoms. Nausea / vomiting and / or diarrhea can be present in about 9% of cases.

These symptoms have so far been one of the most frequent causes of omission or diagnostic delays (11).

5. Unexplained hyposmia, anosmia and dysgeusia could be other symptoms of COVID-19. This issue is currently under investigation (12).

6. Vital signs measurements (do not forget respiratory rate, please) and blood gas analysis in room air, if SpO₂ <94%, at triage or as soon as possible, are essential to correctly assess patients coming to the emergency room (13, 14).
 7. Do not rely only on PO₂ <60 for the diagnosis of respiratory failure, always calculate the PaO₂/ FiO₂ ratio (P/F ratio), especially in young subjects.
 8. Define a “COVID-19 profile” for the rapid order entry of blood tests, including the following tests: blood count, C-RP, creatinine, electrolytes, blood glucose, albumin, AST ALT, LDH, bilirubin, pneumococcal and legionella urinary agents, PT-INR, troponin and procalcitonin.
 9. Chest X-rays have limited sensitivity in 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 (15).
10. Monolateral lung infiltrates do not exclude COVID-19.
They have been described in 25% of cases (15).
11. 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 (16).
 12. 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 (16, 17).
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 (16).

13. History of smoking, respiratory failure, maximum body temperature on admission $\geq 37.3^{\circ}\text{C}$, albuminemia $< 4 \text{ mg/dl}$ would be risk factors for disease progression (severe or critical disease/death).

Results from a multivariate analysis on a small sample (OR ranging from 7 to 15) (18).

14. 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. WHO recommends investigating other pathogens, as co-infections have been reported (2).

15. 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 (2).

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

17. Immediately notify the Public Health Officials of COVID-19 positive patients (use infectious disease notification forms) (19).

3. 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 (14,20) 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 (21).
3. There is no proof that ibuprofen can aggravate COVID-19 clinical picture and the European Medicines Agency is monitoring this issue (22).
4. Start oxygen therapy at 5 L/min and titrate flow rates to reach SpO₂ ≥90% in non-pregnant adults and SpO₂ ≥92-95 % in pregnant patients (2).
5. High-flow nasal oxygen (HFNO) or non-invasive ventilation (NIV, mainly c-PAP) should only be used in selected patients with hypoxemia, 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 (7, 23).
6. 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) (7, 23).
High flow nasal cannulas and non-invasive ventilation are not recommended in viral pandemics, based on studies conducted in influenza and MERS (2).
7. Avoid nebulisation therapies for the potential spread of bacteria.
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 pattern. Nevertheless, the larger particles may cause cough in both patients' and bystanders' and increase the risk of spreading the disease. Nebulisers in patients with pandemic COVID-19 infection have the potential to transmit potentially viable COVID-19 to susceptible bystander hosts (24).

8. 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 (2).

9. Assess thromboembolism and bleeding risk of every patient and provide appropriate thromboprophylaxis.

Consider that recovery times and therefore hypo mobility 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 (2,15).

10. The Respiratory rate, peripheral oxygen saturation (SpO_2) 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.

11. Also monitor white blood cells, lymphocytes and platelets count, LDH, procalcitonin and d-dimer are considered alarm flags (13, 15, 17).

12. Be aware of an eventual development of severe form +/- 7 days after symptom onset (13).

13. If a patient reports a $\text{SpO}_2 \leq 90\%$ in free air or $\leq 92\%$ in conventional oxygen therapy and/or presents ≥ 30 acts/min and/or severe respiratory distress, intensive care therapist consultation must be required (25).

14. Use biosafety precautions when handling oxygen therapy devices (23); cover the patient's face with a surgical mask during HFNO or C-PAP (23); to reduce the risk of aerosolization, possibly use a dual or single circuit non-invasive ventilator with an integrated expiratory valve and a helmet that allows to insert a filter as interface (7).

4. THE 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 decide.

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. (19, 25, 26, 27).

Other important publications (not included among references):

These provide recommendations that can assist in developing local, though may be context specific.

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>

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>

5. RECOMMENDATIONS FOR SURGERY

These recommendations apply to the medical staff of the operating blocks in case COVID-19. Patients with COVID-19 may need to undergo emergency and/or emergency surgery. The following recommendations should be observed (29, 30, 31):

COVID-19 patient positive asymptomatic

1. Surgical team wearing disposable masks, caps and gloves correctly. Anesthesiologist and assistant nurse: FFP2 masks.
2. Patients must wear a medical mask until I.O.T. (oro-tracheal intubation).
3. Airway protection of the patient also intubated with TNT drapes compatible with anesthesiologist assistance.

Symptomatic or having few or minor symptoms positive COVID-19 patient

1. Surgical team wears Personal Protective Equipment (PPE) and FFP2 or FFP3 masks.
2. Anesthesiologist and nurses assigned to direct assistance: FFP2 / FFP3 masks and PPE.
3. Patients must wear a medical mask for the entire time of surgery and / or after the IOT procedure for airway protection with compatible TNT drapes.

Patient COVID-19 sick and in invasive airway management.

1. All professionals must wear PPE and FFP2 / FFP3.

While staying in the operating room it is recommended to utilise laminar flow according to current legislation and post-intervention sanitisation for at least 1 hour.

Team working and 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.

6. RECOMMENDATIONS FOR PREGNANT WOMEN

1. Reduce access of pregnant women to prenatal care, limiting only to high-risk cases (32).
There is no evidence of an increased risk of unfavourable maternal or foetal 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 (33).
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. (32,33).
4. The discharge of mothers after childbirth must follow the recommendations for discharge of COVID-19 or suspected patients (32).
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 expressed breast milk (33). 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 expressing (33). 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 (31). 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 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 (33).

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 (32).

7. For assisting the delivery of women with confirmed or suspected COVID-19, staff must use the safety precautions provided for non-pregnant patients (33).
8. Pregnant women with suspected or confirmed SARS-COV2 infection should be treated with supportive therapies, however taking into account the physiological characteristics of pregnancy (2).
9. 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 foetus, with the consultation of an obstetrician specialist and an ethics committee (2).
10. The decision to proceed to a pre-term birth is based on many factors: gestational age, maternal conditions and foetal stability and requires a collegial evaluation by obstetric, neonatal and intensive care specialists (depending on the mother's condition) (2).
11. Positivity in itself to Coronavirus is not an indication for a caesarean section which in these patients should only be performed based on other obstetric or medical indications (33).
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.

7. 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) (34, 35).
3. A small series of children with COVID-19 has shown a greater prevalence of peripheral halo (halo-sign) lung consolidations on CT (35).
4. 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 (2).
5. Children desaturate more easily during intubation; therefore, it is important to pre-oxygenate with 100% O₂ with a mask with a reservoir before intubating (2).
6. 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 (36, 37).

8. 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 (14, 20) 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) (38)

or

- CURED patient (patient who, in addition to resolving the symptoms, is negative in two consecutive swabs, carried out at least 24 hours apart) (38).

Or

- 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 (38).

Or

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 the appropriate number (in Italy 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 (38).

9. RECOMMENDATION FOR HOME ISOLATION

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:
 - a. promote information
 - b. diffusion of telephone numbers to call in case of occurrence of symptoms
 - c. Arrangements for support e.g. shopping
3. Provide call centres, online chats, FAQs and video tutorials to consult when there is doubt.

10. RECOMMENDATIONS FOR PERSONS IN QUARANTINE (39)

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.

11. RECOMMENDATIONS FOR ONCOLOGIC AND IMMUNOSUPPRESSED PATIENTS

1. Do not indiscriminately discontinue antineoplastic or immunosuppressive therapies. (40-42).
2. In cancer patients, consider the possibility of postponing the treatment cycle on a case-by-case basis (40).
3. Immunosuppressant withdrawal is indicated if symptoms suggestive of infection appear (41); in this case it is good practice to inform the physician responsible for the treatment promptly.
4. Steroids can be continued, but with caution (41).
5. New immunosuppressant prescriptions or dose increases are not recommended during an epidemic (42).
6. Consider the switch from parenteral drugs to others that can be administered at home (e.g. subcutaneously) to reduce access to outpatient clinics (41).
7. Ensure non-deferred outpatient visits and postpone visits for long-term follow-up, after remote evaluation (telephone, email, etc.) (40, 41).
8. Do not allow visitors in therapy rooms and allow the presence of a maximum of one visitor per patient in hospital stays (40).

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

12. 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 (43). 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.

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.

1. 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 (44).
2. At the end of the autopsy investigations, the body must be positioned in a body bag and transported in a refrigerated room.
3. 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.

Disinfection of autopsy rooms

In addition, following an autopsy on a subject with suspect or confirmed COVID-19, the following recommendations for disinfection of autopsy rooms should be applied (45):

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.

Regarding **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.

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 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.

13. PSYCHOLOGICAL SAFETY OF STAFF AND MENTAL WELLBEING OF PATIENTS

Psychological safety of staff (46, 47, 48, 49)

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. 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. 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.

Mental well-being of Patients (50)

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 reliable 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 behaviours 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. Anticipate and counsel about stress reactions.

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 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 (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. MEASURES (51,52,53)

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 / Number of tests performed to hospital staff (as process measure)
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 of Mortality rate

Length of stay measures

1. Length of Stay
2. Average length of stay in ICU of infected
3. Average length of stay in hospital

Process Measures (some examples)

1. Percentage of infected individuals admitted to ICU
2. Percentage of people with comorbidities
3. Percentage of staff with and without correct equipment
4. Number of patients not treated in appropriate level of care
5. Percentage staff trained to use equipment

Balancing measures

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

Patient profiles to consider

- Age
- Gender
- Ethnicity
- Comorbidity
- Region
- Contacts

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

<p>Hydroxy-chloroquine</p>	<p>In association with:</p> <ul style="list-style-type: none"> ▪ Phenylbutazone can induce exfoliative dermatitis ▪ Isoniazid, Amiodarone, Carbamazepine, Phenytoin, Phenothiazide, Ketoconazole and MAO inhibitors (Mono-Amino-Oxidase Inhibitors) can cause hepatotoxicity <p>Effects of hydroxychloroquine on other drugs</p> <ul style="list-style-type: none"> ▪ Anti-epileptics antagonism on anticonvulsant effects ▪ Cyclosporine increased plasma concentrations ▪ Digoxin increased plasma concentration and relative toxicity ▪ Insulin and Antidiabetics potentiation of hypo-glycemic effects
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TABLE 2 - LOPINAVIR/RITONAVIR: Main interactions and recommendations

Co-administered Drug	Mechanism of interaction	Clinical Recommendations
<i>RETROVIRAL AGENTS:</i> <i>Nucleoside reverse transcriptase inhibitors (NRTIs), Non-nucleoside reverse transcriptase inhibitors (NNRTIs), HIV CCR5 - antagonist, Integrase inhibitor, Inhibitors of HIV protease</i>		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.
Antacids		No contraindications
Alpha antagonists		
ALFUZOSIN	Increased concentration (CYP3A inhibition)	Contraindicated (hypotension)
Analgesic Drugs		
FENTANYL	Increased concentration (CYP3A inhibition)	Close monitoring (risk of respiratory)
Antiangular Drugs		
RANOLAZINE	Increased concentration (CYP3A inhibition)	Contraindicated

Co-administered Drug	Mechanism of interaction	Clinical Recommendations
<i>Antiarrhythmics</i>		
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
<i>Antibiotics</i>		
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
<i>Antineoplastics</i>		
<i>Anticoagulants</i>		
WARFARIN	CYP2C9 induction	INR monitoring
RIVAROXABAN	AUC: ↑ 153%, Cmax: ↑ 55% (CYP3A and P-gp inhibition)	Contraindicated (bleeding)

Co-administered Drug	Mechanism of interaction	Clinical Recommendations
VORAPAXAR	Increased concentration (CYP3A inhibition)	Contraindicated
<i>Antiepileptic</i>		
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
<i>Antidepressants and anxiolytics</i>		
TRAZODONE	AUC: ↑ 2,4 times	Dose reduction
<i>Antifungals</i>		
KETOCONAZOLE	Increased concentration (CYP3A inhibition)	Dose reduction

Co-administered Drug	Mechanism of interaction	Clinical Recommendations
<i>Anti-gout</i>		
COLCHICINE	AUC: ↑ 3-times; Cmax: ↑ 1,8-times (CYP3A and/or P-gp inhibition)	Contraindicated
<i>Antihistamines</i>		
ASTEMIZOLE, TERFENADINE	Increased concentration (CYP3A inhibition)	Contraindicated (severe arrhythmias)
<i>Anti-Infectives</i>		
Fusidic Acid	Increased concentration (CYP3A inhibition)	Contraindicated (rhabdomyolysis)
<i>Anti-mycobacterial agents</i>		Specialist Advice
<i>Benzodiazepines</i>		
MIDAZOLAM	Oral administration: AUC: ↑ 13-times parenteral administration: AUC: ↑ 4-times (CYP3A inhibition)	Oral administration contraindicated; close monitoring for parenteral administration

Co-administered Drug	Mechanism of interaction	Clinical Recommendations
<i>Beta2 agonists</i>		
SALMETEROL	Increased concentration (CYP3A inhibition)	Contraindicated (severe cardiovascular event and arrhythmias)
<i>Calcium Channel Blockers</i>		
FELODIPINE, NIFEDIPINE, NICARDIPINE		
<i>Steroids</i>		
DEXAMETHASONE	Reduction of Lopinavir concentrations (CYP3A induction)	Clinical monitoring of anti-viral activity
<i>Phosphodiesterase inhibitors</i>		
AVANAFIL, SILDENAFIL	Increased concentration (CYP3A inhibition)	Contraindicated
<i>Ergot Alkaloids</i>		
DIHYDROERGOTAMINE AND OTHERS	Increased concentration (CYP3A inhibition)	Contraindicated

Co-administered Drug	Mechanism of interaction	Clinical Recommendations
<i>Intestinal Prokinetics</i>		
CISAPRIDE	Increased concentration (CYP3A inhibition)	Contraindicated
<i>Direct anti-HCV agents</i>	Increased plasma concentration (combined mechanisms)	Contraindicated
<i>HCV protease inhibitors</i>		Contraindicated
<i>Immuno-suppressers</i>		
CICLOSPORINE	Increased concentration (CYP3A inhibition)	Plasma level monitoring
<i>Statins</i>		Contraindicated; fluvastatin and pravastatin tolerated
<i>Opioids</i>		
METHADONE	Decrease in concentration	Plasma level monitoring
<i>Contraceptives</i>		
Ethinylestradiol	Decrease in concentration	Use additional contraceptive methods

Co-administered Drug	Mechanism of interaction	Clinical Recommendations
<i>Hormone Replacement Therapy (HRT)</i>		
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

Co-administered drug	Interaction mechanism	Clinical recommendations
<i>Anti-retroviral agents (HIV)</i>		
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
<i>CCR5 A ntagonists</i>		No dose adjustment necessary
MAVAVIROC	Increased concentration (CYP3A inhibition)	Specialist advice for dose adjustment
<i>AI / M or calcium carbonate-based antacids</i>		No dose adjustment
<i>Alpha antagonists</i>		
ALFUZOSIN	Increased concentration (CYP3A inhibition)	Contraindicated (hypotension)

Co-administered drug	Interaction mechanism	Clinical recommendations
<i>Anaesthetic</i>		
AL FENTANYL	Increased concentration (inhibition of CYP3A4)	Dose reduction and monitoring (respiratory depression risk)
<i>Antianginal/tymic antiaries</i>		
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
<i>Antibiotics</i>		
Clarithromycin	Increased AUC (CYP3A inhibition)	Caution dose adjustment in patients with renal impairment CrCL <30 ml / min

Co-administered drug	Interaction mechanism	Clinical recommendations
<i>Anticoagulants</i>		
WARFARIN	Theoretical mechanism of alteration of plasma concentrations	INR monitoring
APIXABAN, EDOXABAN, RIVAROXABAN	Increased plasma concentrations (inhibition of CYP3A & P-gp)	contraindicated
DAPIGATRAN; ticagrelor	Increased plasma concentrations (inhibition of CYP3A & P-gp)	contraindicated
<i>Anticonvulsants</i>		
clonazepam	Increased concentration (CYP3A inhibition)	Clinical monitoring
CARBAMAZEPINA, FENOBARBITALE, FENITOINA	Reduced concentrations of darunavir and/or cobicistat (CYP3A induction).	Contraindicated
<i>Antidepressants and anxiolytics</i>		
ST. JOHN'S GRASS	Reduction of darunavir and / or cobicistat concentrations (CYP3A induction).	contraindicated

Co-administered drug	Interaction mechanism	Clinical recommendations
PAROXETINE, SERTRALINA, AMITRIPTILINA, DESIPRAMINA, IMIPRAMINA, NORTRIPTILINA, TRAZODONE	Increased plasma concentrations (CYP2D6 and/or inhibition CYP3A)	Dosage reduction and clinical monitoring
<i>Antidiabetic</i>		
METFORMIN	Increased plasma concentration	Dosage reduction and clinical monitoring
Co-administered drug Interaction mechanism Clinical recommendations		
<i>antiemetics</i>		
DOMPERIDONE	Not studied	contraindicated
<i>Anti-fungals</i>		
CLOTRIMAZOLO, FLUCONAZOLO, ITRACONAZOLO, ISAVUCONAZOLO, POSACONAZOLO	Increased concentration (inhibition of CYP3A &/or P-gp)	Caution, clinical monitoring and dosing Voriconazole contraindicated
<i>Anti-gout</i>		
colchicine	Increased concentration (inhibition of P-gp and/or CYP3A4)	Dosage reduction, contraindicated in the presence of hepatic or renal impairment

Co-administered drug	Interaction mechanism	Clinical recommendations
<i>H2 receptor antagonists</i>		No dose adjustment necessary
<i>Antimycobacterials</i>		Specialized evaluation, tendentially contraindicated
<i>Anti-psychotics / neuroleptics</i>		
PERFENAZINA, RISPERIDONE, TIORIDAZINA	Increased plasma concentrations (inhibition of CYP3A, CYP2D6 and/or P- gp)	Dose reduction and clinical monitoring
LURASIDONE, PIMOZIDE, SERTINDOLO, QUETIAPINA		Contraindicated
<i>Anti-cancer</i>	Theoretical mechanism of concentration increase (CYP3A inhibition)	Specialist evaluation, extreme caution
<i>Beta2 agonists</i>		
SALMETEROL	Increased concentration (CYP3A inhibition)	Contraindicated (serious cardiovascular adverse events, arrhythmias)
<i>Beta blockers</i>		
CARVEDILOL, METOPROLOL, TIMOLOL	Plasma concentrations increased (CYP3A inhibition)	Dose reduction and clinical monitoring

Co-administered drug	Interaction mechanism	Clinical recommendations
<i>Calcium antagonists</i>		
AMLODIPINA, DILTIAZEM, FELODIPINA, NIFEDIPINA, NICARDIPINA, VERAPAMIL	Increased concentration (inhibition of CYP3A and / or CYP2D6)	Dose reduction and clinical monitoring
<i>Corticosteroids</i>		
dexamethasone	Reduction of Darunavir and / or cobicistat concentrations (CYP3A induction)	Caution
<i>Proton pump inhibitors</i>		
		No dose adjustment
<i>Inhibitors of phosphodiesterase</i>		
TADALAFIL, SILDENAFIL	Increased concentration (CYP3A inhibition)	Contraindicated
<i>Antivirals direct action against HCV (inhibitors NS3-4A protease)</i>	Increased plasma concentrations (combination of mechanisms)	Contraindicated
<i>Endothelial receptor antagonists (Bosentan)</i>	Increased concentration (theoretical consideration)	Contraindicated

Co-administered drug	Interaction mechanism	Clinical recommendations
<i>Immunosuppressant</i>		
CYCLOSPORINE	Increased concentration (CYP3A inhibition)	Monitoring of drug levels
everolimus		contraindicated
<i>Narcotics, Opioids</i>		
METHADONE	Increased concentration (theoretical consideration)	Monitoring of drug levels
Buprenorphine / naloxone	Increased concentration (theoretical consideration)	Clinical monitoring
FENTANYL, OXYCODONE, TRAMADOL	Increased concentration (theoretical consideration)	Clinical monitoring
<i>Opioid antagonists</i>		
NALOXEGOL	Not studied	contraindicated
<i>Sedatives / hypnotics</i>		
BUSPIRONE, CLORAZEPAM, DIAZEPAM, ESTAZOLAM, FLURAZEPAM, ZOLPIDEM	Increased concentration (CYP3A inhibition)	Caution, dose reduction and clinical monitoring

Co-administered drug	Interaction mechanism	Clinical recommendations
MIDAZOLAM (PARENTERAL)		Only in intensive care.
MIDAZOLAM (ORAL)		contraindicated
<i>Urological drugs</i>		
FESOTERODINA, SOLIFENACINA	Not studied	Caution, dose reduction and clinical monitoring
DAPOXETINE	Not studied	Contraindicated
<i>Contraceptives</i>		
	Alteration of plasma concentrations	Use additional methods of contraception
drospirenone		Monitoring for possible hypokalaemia
<i>Statins and other</i>		
<i>hypo-lipidemic agents</i>		
(Lomitapide)		

TABLE 4 Serious adverse effects

	Lopinavir / Ritonavir	Darunavir / cobicistat	Chloroquine	Hydroxychlor oquine	Tolicizumab
Serious adverse effects	Hypersensitivity reaction, angioedema Stevens-Johnson syndrome / Toxic epidermal necrolysis / Erythema multiforme QT prolongation & Torsade de Pointes AV block, PR prolongation Hyperglycaemia, hypertriglyceride mia Renal failure Anemia, leukopenia, neutropenia Pancreatitis Hepatotoxicity	Hepatotoxicity Anorexia, hyper-cholesterol-aemia hyper-triglyceridemia Renal failure	QT prolongation & Torsades de Pointes Reduction in seizure threshold Anaphylaxis or anaphylactoid reaction Neuromuscular impairment Neuropsychiatric disorders (potential to increase delirium) Pancytopenia, neutropenia, thrombocytopenia, aplastic anemia Hepatitis	Hypoglycemia QT prolongation Cardio-myopathy Muscle asthenia Retinal or visual field alterations Skin reactions Oral ulcerations Complicated diverticulitis Hepatotoxicity	Interstitial pneumonia Infections Leukopenia, neutropenia hypo- fibrinogenaemia Upper respiratory infections Herpes simplex and zoster Hepatotoxicity

	Lopinavir / Ritonavir	Darunavir / cobicistat	Chloroquine	Hydroxychlor oquine	Tolicizumab
Common adverse reactions	Nausea / vomiting, diarrhoea Insomnia, anxiety	Nausea / vomiting, diarrhoea Insomnia, anxiety Headache Rash Muscle Pain	Nausea / vomiting, diarrhoea, abdominal pain Visual disturbance, headache Extrapyramida l symptoms	Nausea / vomiting, diarrhoea, abdominal pain Visual disturbance, headache Skin rash, itching Extra-pyramidal symptoms	Hypertension Headache Skin reactions Conjunctivitis Hyper- cholesterolemia Abdominal pain, gastritis Cough, dyspnoea
Contra- indicated in:	Cardiac disease ischemic heart disease, cardiomyopathy, structural heart disease, QT prolongation Liver disease	Liver failure (class C Child- Pugh) Haemophilia	Porphyria G6PD deficiency Epilepsy Heart failure Recent myocardial infarction	Porphyria Retinopathy Maculopathies Children <6a <31 Kg	Administration of alive or attenuated vaccines
Monitor	Transaminases	Kidney function	Serial complete blood count QT interval	Blood count, glycemia, QT interval	Cholesterol, blood count, transaminases