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Clinics and Research in Hepatology and Gastroenterology (2020) 44, 275—281

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Suggestions for the care of patients with liver disease during the Coronavirus 2019 pandemic

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Available online 22 April 2020

KEYWORDS
COVID-19;
Chronic liver disease;
SARS-CoV-2;
Cholangiocytes

Summary This document, written by the French Association for the Study of the Liver (AFEF) board, aims to provide information to physicians involved in the care of patients with liver disease during the Coronavirus disease (COVID-19) epidemic. These are not based on a systematic review of the literature and a rigorous evaluation using the GRADE method. These are recommendations based on feedback from China available in the form of original articles or letters — for which the scientific evidence is often modest — and the rules put forward by American (1) and European (Boettler et al, 2020) hepatology societies, the French National Digestive Cancer Thesaurus (Di Fiore et al., 2020) and the Francophone Transplantation Society (4). These suggestions require adjustment according to the geographical particularities of the epidemic, available standard procedures and access to local resources. This document will be updated as regularly as possible according to the evolution of our knowledge and characteristics on the epidemic.

General Information on liver and COVID-19

COVID-19 disease, linked to the SARS-CoV-2 virus, is rapidly spreading around the world. Following the city of Wuhan and the province of Hubei, European healthcare systems are facing an outbreak of seriously ill patients, but few are fully equipped to deal with this health crisis. In this totally unprecedented and unexpected context, we must readapt the procedures with respect to the care of patients with liver disease. The aims of this document are to examine what is currently known about the relationship between COVID-19 and the liver, and to anticipate the safest possible care procedures in order to reduce the impact of the pandemic on patients with liver disease.

Feedback from China indicates:

- the presence of underlying chronic liver disease in 2—11% of patients cared for with COVID-19 infection [5];
- an increase in transaminase levels in 25—35% of patients, generally moderate (median 23—39 UI/L), with higher lev-

https://doi.org/10.1016/j.clinre.2020.04.001
2210-7401/

els in symptomatic and/or severe forms and/or requiring intensive care hospitalisation [5,6] and/or fatalities [7]. To date the mechanism involved is unclear. Indeed, data suggesting the possibility of localisation of the virus in the liver are preliminary, and it is plausible that elevated liver enzymes in the context of COVID-19 infection could be related to the inflammatory response syndrome, drug induced toxicities (paracetamol, antibiotics), and ischemia liver or viral myocarditis frequent in this situation. Moreover, serological testing for hepatotropic viruses is recommended in this situation;

- the expression of SARS-CoV-2 receptor (the angiotensin-converting enzyme 2 receptor) by cholangiocytes [8];
- the fact that populations believed to be at risk for severe forms of COVID-19 include patients with cirrhosis, those with autoimmune hepatitis on immunosuppressive drugs, and pre- and post-transplant patients on immunosuppressive therapy [9].

We propose here recommendations based on feedback from China and the rules put forward by American [1] and European [2] hepatology societies, the French National Digestive Cancer Thesaurus [3] and the Francophone Transplantation Society [4]. In addition to the classical barrier precautions (regular hand washing with soap and water and/or use of alcohol-based gel, discarding handshakes and hugs), the extension of expired prescription administration into the 1st quarter of 2020 (until May 31st, according to the Decree of 1 April 2020) and the implementation of social isolation and home confinement since the 17th March, other simple measures are suggested such as, for example, adapting patient follow-up for stable patients, ideally by tele or video consultation, automatic temporary cessation of employment for fragile patients whose employment would be incompatible with teleworking (https://solidarites-sante.gouv.fr/IMG/pdf/arret-travail-covid-19_2.pdf), the direct admission of patients to non-COVID units and the withdrawal of visits from relatives to hospitalised patients.

Recommended Care

Patients WITHOUT signs suggestive of COVID-19

Aims	Protect patients against SARS-CoV-2 and continue their care in safe conditions by avoiding their movement. Free healthcare facilities of their functions to allow them to receive and concentrate their medical and paramedical resources on serious patients (with or without COVID-19).
Potential adjustments to etiological treatment of liver diseases	***HBV***: continuation of ongoing analogous treatments or initiation them in emergency cases (cirrhosis, reactivation) or in situations of high transmission risk (drug users, migrants living in crowded conditions, etc.). ***HCV***: continue ongoing direct anti-viral treatments; as a general rule, defer treatment initiation until the end of social isolation in waiting patients by repeating the barrier precautions, except in emergency situations (high risk of transmission such as on-going drug users, migrants living in overcrowded conditions, etc.). ***HDV:*** continue ongoing Bulevirtide therapy in combination or not with interferon-α in the temporary use authorisation cohort framework; as a general rule, postpone therapy initiation until the end of social isolation in waiting patients. It is recommended to repeat the advice regarding strict patient confinement and barrier precautions, to delegate if possible to a third party the monthly retrieval of treatments from the hospital pharmacy (if the latter cannot dispatch them) and to carry out monthly check-ups during home visits by a registered nurse. ***Alcohol***: advise on consumption moderation including 2 days of abstinence per week, and not to take advantage of the confinement to begin an abrupt withdrawal that could require hospital care. ***NASH***: repeat the advice on strict confinement and barrier precautions in patients with component(s) of metabolic syndrome at risk of severe form of COVID-19 such as morbid obesity or diabetes [9]. ***Genetic haemochromatosis***: 1. Attack phase treatment: continue periodic phlebotomies. Ideally as blood donations at the French Blood Authority (EFS), otherwise if possible, at home by a registered nurse; defer the initiation or resumption of bloodletting until the end of confinement. 2. Maintenance phase treatment: defer phlebotomies until the end of social isolation. ***Rare liver diseases (Autoimmune Hepatitis, PBC, PSC, Wilson, etc.):*** 1. On-going immunosuppressive treatments: Continue without change of dosage. 2. Treatment initiation for acute autoimmune hepatitis: discuss on a case-by-case basis according to the regional epidemic, if necessary, together with local Competence Centres. The option preferred for AIH treatment by the French Reference Centre is corticosteroid therapy (prednisolone 0.5 mg/kg/day or budesonide 9 mg/day for non-severe forms) with delayed onset of other immunosuppressive regimens as a general rule. ***Liver transplant recipients:*** continue immunosuppressive therapy without change [4].

Stable patients/outpatients

Without advanced hepatic fibrosis or liver-related complications.

Temporary cessation of professional activity	Exclusively for patients with comorbidity(ies) [9] whom employer cannot guarantee the possibility of teleworking (https://solidarites-sante.gouv.fr/IMG/pdf/arret-travail-covid-19_2.pdf).
Consultations	Adaptation of non-urgent follow-up consultations initially planned face-to-face =>Reorientation towards safe healthcare with respect to the risk of infection (Tele or video consultation) in order to avoid disruptions in follow-up. +Automatic extension of prescriptions with pharmacists +Home visits by a registered nurse if needed

With advanced hepatic fibrosis or liver-related complications.

Temporary cessation of employment	Recommended for an initial period of 21 days if the employer cannot guarantee the possibility of teleworking (https://solidarites-sante.gouv.fr/IMG/pdf/arret-travail-covid-19_2.pdf).
Consultations	Presence not required: Adaptation of non-urgent follow-up consultations initially planned face-to-face =>Reorientation towards safe healthcare with respect to the risk of infection (Tele or video consultation) in order to avoid disruptions in follow-up. +Home visits by a registered nurse on medical prescription if needed +Automatic extension of prescriptions with pharmacists acting on medical advice in the case of polypharmacy (> 5 drugs) or renewal of treatment within 3 months. Continuation of primary or secondary prophylaxis in patients with ascites, clinically significant portal hypertension and/or encephalopathy is essential to avoid hospitalisation. Presence required (diagnosis and pre-treatment consultations for liver cancer, new patients with clinically significant signs: jaundice, increased serum ALAT level > 10 times the upper limit of normal values, recent hepatic decompensation) Screening for signs of COVID-19 before coming to the hospital and at the reception desk (+body temperature taken at arrival), and if in doubt, screen for COVID-19 ideally before arriving in the department according to the facility's standard procedures. Having patients wear a surgical mask (resources permitting) as soon as they arrive at the medical facility. Implementation of barrier precautions: disinfect equipment (seats, handles, etc.) between each patient, avoid waiting in groups, reduce waiting times in waiting rooms, eliminate newspapers, maintain a minimal 1 metre distance between patients, frequently ventilate waiting rooms, enforce as strongly as possible the rules concerning hygiene and protection of nursing staff.
Scheduled day and short-stay admissions	Reschedule stays and/or non-urgent procedures =>In regions heavily impacted by the outbreak (peak or plateau phases), carried out in urban areas by mobilising available resources otherwise postpone with an approximate average delay of 1 to 2 months: - periodic surveillance imaging of previous HCC or current HCC under treatment; - biannual screening for HCC in high risk patients; - non-urgent liver biopsies; - measurements of liver stiffness and/or CAP. It is cautious to defer pre-transplant check-ups when possible according to the risk/benefit balance, or to perform most tests outside the hospital depending on local resources. - Maintenance of scheduled stays within non-COVID units by ensuring that before each admission patients do not present any signs of COVID-19 and by being extra careful to protect them (surgical mask as soon as they arrive in the facility, implement barrier precautions with avoidance of waiting in groups, especially at admissions and in waiting rooms, reduce waiting times, single rooms when possible, maintain a minimal 1 metre distance between patients, apply hygiene rules for the nursing staff and limit the number of health carers involved) for the following main indications: -1/ curative treatments of primary liver cancer (surgery and interventional radiology) [3]; -2/ ascites paracentesis; -3/ esophageal variceal ligation and gastric variceal sclerotherapy in secondary prevention; -4/ urgent liver biopsies.

Clinical trials	- Defer inclusions to the end of confinement if possible, except for COVID-19 trials and non COVID-19 observational trials (assessment of individual benefit/risk balances). - On a case-by-case basis, evaluate with the promoter the possibility of carrying out remote consultations, blood sampling at home by registered nurses and home dispatching of the treatments under investigation.
Vaccinations	In the absence of immunization against pneumococcus: carry out pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed) if this does not jeopardise confinement, otherwise defer it until the end of social isolation.

Patients requiring traditional hospitalisation

Action to be taken	Hospitalise in a NON COVID-19 unit/department: - ensuring before each admission that patients present no signs of COVID-19 and taking patient temperature on arrival; - performing a thoracic CT scan to screen for COVID-19 prior to admission in the event of unexplained recent hepatic decompensation [2]; - favouring direct admissions without prior passage to the emergency department; - taking all measures to avoid contamination (surgical mask for all patients as soon as they arrive in the unit, hand washing using alcohol-based gel, implement barrier precautions with avoidance of waiting in groups, particularly at admissions, reduce waiting times, maintain a minimal 1 metre distance between patients, apply hygiene rules for nursing staff, limit the number of nursing staff involved in care and visits if they remain authorised. NB: These very strict measures have proven their effectiveness in terms of mortality among 111 Chinese patients with decompensated cirrhosis, 2/3 of whom were hospitalised and 1/3 ambulatory [10].

Patients WITH Signs Suggestive of COVID-19

Aim	Protect, as much as possible, healthcare staff and NON-COVID patients from SARS-CoV-2 contamination by caring for patients under safe conditions.
Potential adjustments of etiological treatment of the liver disease	***HBV***: continue on-going analogous treatments or their initiation in emergency situations (cirrhosis, reactivation) if the patient's condition permits. ***HCV***: continue on-going direct antiviral treatments if the patient's condition permits, but defer treatment initiation in waiting patients. ***HDV***: continue (or decrease in dosage) on-going anti-viral treatments with Bulevirtide in combination or not with interferon-α in the Temporary Use Authorisation cohort framework on a case-by-case according to the severity of COVID-19 and its impact on liver disease (individual risk-benefit balance). If outpatient treatment continues, it is imperative to repeat the strict advice with regards to confinement and barrier precautions, to delegate if possible to a third party the monthly retrieval of treatments from the hospital pharmacy, and to have monthly check-ups carried out at home by a registered nurse in the absence of hospitalisation. For patients with impaired renal function (clearance < 60ml/min), and/or decompensated liver disease, Bulevirtide should be discontinued. ***Alcohol***: repeat advice on consumption moderation including at least 2 days of abstinence per week and if possible not to begin an abrupt withdrawal. ***NASH***: remain alert as many of these patients are at risk for the severe form (if they have component(s) of metabolic syndrome(s) listed in reference 9). ***Genetic hemochromatosis***: temporarily stop phlebotomies. ***Rare liver diseases (Autoimmune Hepatitis, PBC, PSC, Wilson, etc.)***:

The possible continuation or reduction in dosage of immunosuppressive treatments must be discussed on a case-by-case basis according to the severity of COVID-19 infection and the individual benefit/risk balance with the internist/infectious disease specialist/intensive care staff on one hand and the hepatologist on the other hand, together if necessary with the help of local Competence Centres or the French Reference Centre.
For corticosteroids, a decrease in dosage may be discussed if necessary but maintaining a dose of at least 10 mg/day to avoid adrenal insufficiency.
Other immunosuppressants, such as azathioprine (Imurel®) or mycophenolic acid (Cellcept®) may be reduced if necessary, especially in patients with lymphopenia, bacterial or fungal superinfection, or lung aggravation related to COVID-19.

Liver transplant recipients[4]:
1.Outpatient or Inpatient with Symptomatic COVID-19 Not Presenting Severe Form Signs (not requiring oxygen)
1.1 - Patients < 1 year since transplantation
- Discontinue corticosteroid treatment unless there is a high immunological risk of rejection or recurrence of autoimmune disease, in which case the corticosteroid needs to be reduced and maintained at 5 mg/day.
- Discontinue mycophenolic acid (Cellcept® or Myfortic®) or azathioprine (Imurel®) immunosuppressive therapy and resume after viral recovery at the same dose prior to cessation.
- Continue treatment with tacrolimus with target residual blood concentrations between 4-8 ng/mL, or continue treatment with cyclosporin with target residual blood concentrations between 100-150 ng/mL or target blood concentrations between 400-600 ng/mL at 2 hours after intake (C2).

For patients treated with mTOR inhibitors:
- For patients under tacrolimus + mTOR inhibitor dual therapy: discontinue mTOR inhibitor (Rapamune® or Certican®) treatment and resume treatment following recovery at the same dose prior to cessation, maintenance of tacrolimus treatment with target residual blood concentrations between 4 and 8 ng/mL.
- For patients under mycophenolic acid (Cellcept® or Myfortic®) + mTOR inhibitor dual therapy: halve the dosage of mycophenolic acid and continue of mTOR inhibitor (Rapamune® or Certican®) treatment with target residual blood concentrations between 4 and 6 ng/ml, resumption after recovery at the same dose prior to cessation.

1.2 - Patients > 1 year since transplantation
- Patients treated with corticosteroid treatment due to a high immunological risk of rejection or recurrence of autoimmune disease: maintain corticosteroids (same dose).
- Discontinue mycophenolic acid (Cellcept® or Myfortic®) treatment and resumption after recovery at the same dose prior to cessation.
- For patients treated with calcineurin inhibitors, maintain tacrolimus and cyclosporin at the same doses.
- For patients treated with mTOR inhibitors:
-1. For patients under tacrolimus + mTOR inhibitor dual therapy: discontinue mTOR inhibitor (Rapamune® or Certican®) treatment and resume treatment following recovery at the same dose prior to cessation, maintain tacrolimus and cyclosporin treatments at the same doses.
-2. For patients under mycophenolic acid (Cellcept® or Myfortic®) + mTOR inhibitor dual therapy: discontinue mycophenolic acid treatment and resume treatment following recovery at the same dose prior to cessation, continuation of mTOR inhibitor treatment at the same dose.
-3. For patients under mycophenolic acid (Cellcept® or Myfortic®) or mTOR inhibitor monotherapy: continue treatment at the same doses.

1.3—In all cases
- Resumption of pre-infectious episode treatment from day14 of symptom onset.
- Daily self-monitoring (temperature, dyspnea, chest pain).
- Regular phone calls from the doctor with patient responsibility (for example: day 3, then day 7 - important given it corresponds to the acute phase).
- Home confinement for up to 10 days after onset of symptoms.
- Outings with a mask until day 14 after onset of symptoms.

2. COVID-19 Inpatient Requiring Oxygen and/or Lymphophenic
- Maintain corticosteroids at a dose of 10 mg/day (prednisone equivalent).
- Discontinue remaining immunosuppressive therapy.
- If the patient is at high immunological risk or close to the transplant date and does not present lymphopenia:

	1/ Continue treatment with calcineurin inhibitors with target residual blood concentrations between 4 et 8 ng/mL for tacrolimus and 100-150 ng/ml (C_0) and 400-600 ng/mL at 2 hours after intake (C2) for cyclosporin. 2/ Resume pre-infectious episode treatment as soon as oxygen therapy is withdrawn.
	3. Severe COVID-19 Infection with Acute Respiratory Distress Syndrome - Maintain corticosteroids at a dose of 10 mg/day (prednisone equivalent). - Discontinue remaining immunosuppressive therapy. - Resume tacrolimus at 3-5 ng/mL dosages within 72 hours of ventilation withdrawal. Resume pre-treatment as soon as viral recovery occurs, taking into account the prolonged duration of viral excretion.
General mesures	- Limit the use of paracetamol for antipyretic purposes to 2-3 g/day, especially for patients with cirrhosis and/or with excessive alcohol consumption. - Formally contraindicate the use of NSAIDs. - Verify that there are no drug interactions between the standard treatment for liver disease and those used for COVID-19 (*Annex*). Due to the potentially severe liver damage among some patients, the magnitude of these interactions may be significant and caution must be taken. - Limit diagnostic or therapeutic endoscopies to emergencies (gastrointestinal haemorrhage, bacterial cholangitis or other vital emergencies) - Optimise nutritional care with the prescription of at least 3 oral nutritional supplements per day for all patients who cannot eat except those in intensive care unit and with limited care [11].

Patients without advanced hepatic fibrosis or liver-related complications
These patients should receive the same care as the general population. Without signs of severe COVID-19, these patients should be cared for at home under strict confinement.

Patients with advanced liver disease or acute hepatitis not requiring hospitalisation
In suspected COVID-19, the need or not for hospitalisation should be confirmed by the attending physician and/or staff within the emergency unit and/or emergency medical services.

These patients need to be tested by PCR and/or thoracic CT [12]. Without signs of severe COVID-19 infection, these patients should be cared for at home in isolation with close monitoring.

Follow-up procedures should be decided based on medical assessment:

- simple self-monitoring of symptoms without the need for planning further consultation;
- medical follow-up (tele or video consultation preferred if possible) between Day 6 and Day 10 for monitoring;
- reinforced follow-up at home by a registered nurse for patients at risk being unable to self-monitor.

If a patient does visit for consultation, they must notify the healthcare staff of their arrival, report their condition and wear a mask as far upstream as possible in general procedures.

Patients With Advanced Chronic Liver Disease or Acute Hepatitis Requiring Hospitalisation for Liver-related Complications
These patients should be cared in a COVID-19 unit/department, if possible within the facility where the patient is already known and routinely followed-up and with the hepatology team that usually takes care of them.

Disclosure of interest

Nathalie Ganne-Carrié: Bayer, Gilead, Ipsen, Roche, Shionogi. Hélène Fontaine: Abbvie, Gilead, MSD. Jérôme Dumortier: Novartis, Astellas, Chiesi, Abbvie, Gilead, Intercept. Jérôme Boursier: Abbvie, BMS, Echosens, Gilead, Intercept, Inventiva, Siemens. Christophe Bureau: Abbvie, Gilead, Gore. Vincent Leroy: Abbvie, Gilead, Intercept, Siemens Marc Bourlière: Merck, Janssen, Gilead, Boehringer Ingelheim, BMS, Novartis, Roche, Abbott, GSK, Vertex, Idenix, Intercept.

Appendix. Assessing the Risk of Drug Interactions between Liver Disease Treatments and COVID-19 Treatments

Hepatitis B Treatments.

anti-HBV antiviral/COVID-19 treatment	Remdesivir	Lopinavir/Ritonavir	Hydroxychloroquine
Tenofovir disoproxil	Weak interaction risk	Moderate interaction risk—Increase concentrations of tenofovir — Renal function monitoring	Weak interaction risk
Entecavir	Weak interaction risk	Weak interaction risk	Weak interaction risk

Hepatitis C Treatments.

anti-HCV antiviral/COVID-19 treatment	Remdesivir	Lopinavir/Ritonavir	Hydroxychloroquine
Sofosbuvir 400 mg + Velpatasvir 100 mg	Weak interaction risk	Weak interaction risk	Weak interaction risk
Sofosbuvir 400 mg + Velpatasvir 100 mg + Voxilaprevir 100 mg	Weak interaction risk	Increase concentrations of Voxilaprevir - Association not recommended	Low to moderate interaction risk — Cardiac ECG monitoring and therapeutic drug monitoring of hydroxychloroquine concentrations
Glecaprevir 100 mg + Pibrentasvir 40 mg	Weak interaction risk	Increase concentrations of Glecaprevir and Pibrentasvir - Association not recommended	Moderate interaction risk — Cardiac ECG monitoring and therapeutic drug monitoring of hydroxychloroquine concentrations

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