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## Highlights for management of patients with Autoimmune Liver Disease during COVID-19 pandemia

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Dear Editor,

Although 2019 coronavirus (Covid-19) infection is mainly characterised by respiratory symptoms that can progress to acute respiratory distress syndrome (ARDS) [1, 2], abnormalities in liver enzymes have been reported during severe infections [3]. As the outbreak of Covid-19 became pandemic, many liver centres worldwide have faced the challenge of management of patients with liver diseases [3] and concerns have been raised particularly for immunocompromised patients. This is mainly based on previous data on the higher risk of severe respiratory viral infections in patients treated with immunosuppressive medications [4, 5]. However, preliminary experience from Bergamo, Lombardy, suggests that immunosuppressed patients are not at increased risk during Covid-19 infection [6]; also, Chinese data from the epicentre of the infection show that even patients with chronic liver disease where only a minority among those infected with Covid-2019 [2].

One area of major concern are patients with autoimmune liver diseases (AILDs), particularly those with autoimmune hepatitis (AIH) or cirrhosis receiving immunosuppressive therapy, due to the lack of evidence-based treatment recommendations. This may lead to an empirical reduction of immunosuppressive agents, particularly antimetabolites, which is probably not justified. We herein present a brief description of the management protocol developed and implemented for patients with AILD in three referral centres in Europe during the present pandemic (**Figure 1**).

Patients should be stratified based on risk of complications in order to avoid unnecessary access to the hospital. Indeed, patients with stable chronic AILD on long-term therapy are at low risk of complications and/or progression. While available data may suggest that immunosuppressed patients are not at increased risk of ARDS [6], a flare of AIH secondary to unnecessary drug reduction/withdrawal, would require a higher dose of steroids and thus potentially increased risk of infection. In this low-risk scenario, we suggest to: (i) postpone follow-up visits until the emergency is over; (ii) be proactive in sending general information and recommendations to your patients (i.e. mailing list) ahead of time; (iii) use web-based consultation upon request in addition to telephone-based consultations; and, (iv) organize drug dispensation with the local pharmacy for therapy maintenance.

Patients with an already established liver cirrhosis, of any cause, that present with an acute complication are at high risk of morbidity and mortality independent of the viral epidemic. Indeed, severe flares of AIH, obstructive jaundice in Primary Sclerosing Cholangitis (PSC), severe cholangitis, and/or gastrointestinal (GI) bleeding are associated with high short-term mortality and thus require urgent care and treatment. Even though the risk of Covid-19 infection in fragile patients who access the hospital seems to be relatively high, the

underlying liver disease in these patients presents such a high-risk condition in itself that hospital care is mandatory. We therefore suggest to: (i) organize an independent flow for urgent access to the hospital in order to avoid any contact with Covid-19 positive patients (e.g. avoid access through the general emergency department); (ii) limit invasive procedures such as endoscopy to emergency interventions avoiding screening, and follow local protocols in case of emergencies (i.e. obstructive jaundice, bleeding) [7]; (iii) start standard therapy at the usual dose for treatment of acute flare of AIH; (iv) coordinate care in case of hepatic failure with the regional Transplant Centre; finally, (v) in case of infection reduce immunosuppression - particularly antimetabolites in those with lymphopenia - and be timely in tapering steroids. Careful hospital hygiene procedures should be followed, and outpatient follow-up care organised in order to keep hospitalization as short as absolutely necessary.

Finally, conditions at medium risk, including acute onset of symptoms in non-cirrhotic patients and chronic management of decompensated cirrhotic patients, should be consciously evaluated and managed aiming to avoid unnecessary access to the hospital [8]. Although there is no available data, we indeed work under the assumption that pulmonary infection due to Covid-19 might have a worse outcome in these fragile population. Non-cirrhotic clinically stable patients that present with abnormal liver test should: (i) defer invasive diagnostic procedures that require access to the hospital (i.e. liver biopsy); (ii) start empiric (i.e. steroids in AIH) therapy using web-based consultation; and, (iii) establish a short term web-based follow-up to define drug efficacy and adapt treatment accordingly. Thus, in this particular situation the diagnosis of AIH may be given without histology, if typical biochemical and serological results are followed by a convincing treatment response. Prove of the diagnosis can be undertaken later, either by a relapse upon therapy reduction, or a follow-up liver biopsy when conditions are safer. As already reported in China [8], advanced liver cirrhosis and decompensated patients, can be monitored with a web-based system and all non-urgent medical visits should be postponed until the emergency is over. Urgent procedures (i.e. paracentesis) should be organised using a Covid-free path in the hospital, another Covid-free facility or home care. Finally, we recommend strict adherence to standard social distancing protocols and social isolation and emphasise, in cirrhotic patients, the importance of vaccination for *Streptococcus pneumoniae* and *seasonal flu* and of reinforcing social distancing measures. Further data are needed in order to demonstrate the real impact of Covid-19 infection in immunocompromised patients. Until then, and while vaccination is not available, we suggest continuing a cautious approach during low-level seasonal persistence of Covid-19 in the years to come.

Although we cannot currently evaluate the efficacy of our management protocol, we believe this framework might be a useful tool for management of AILD for the time being, including prevention of Covid-19 infection, especially in non-referral centres

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**ACUTE AUTOIMMUNE LIVER DISEASE****CHRONIC AUTOIMMUNE LIVER DISEASE**

NON-CIRRHOSIS

**CURRENT KNOWLEDGE:**

- AIH may present acute onset and jaundice in non cirrhotic patients
- Mild alteration of liver tests in non cirrhotic patients are not associated with a high risk of progression

**LIVER CLINIC:**

- Avoid invasive diagnostic procedures that require access to the hospital (i.e. liver biopsy)
- Start empiric therapy using web-based consultation
- Establish a sort term web-based follow-up to define drug efficacy

**PATIENTS:**

- Avoid contact with anybody who has symptoms of a respiratory infection
- Minimise the time any infected household spend in shared spaces
- Wash your hands often
- Strictly respect isolation protocols
- Contact your GP and/or hepatologist in case respiratory symptoms or fever

**CURRENT KNOWLEDGE:**

- Immunosuppressed patients do not seem to be at increased risk of acute respiratory distress syndrome
- a flare of autoimmune liver disease would require a high dose of steroids and potentially increased risk

**LIVER CLINIC:**

- Postpone medical visits until the emergency is over
- Send general information and recommendations to your patients (i.e. mailing list, medical association, ERN)
- Use web-based consultation upon request
- Organize drug dispensation with the local pharmacy

**PATIENTS:**

- Continue immunosuppressive drugs in unchanged doses
- Wash your hands often
- Avoid contact with anybody who has symptoms of a respiratory infection
- Strictly respect isolation protocols
- Minimise the time any infected household spend in shared spaces
- Contact your GP/hepatologist in case of respiratory symptoms or fever

CIRRHOSIS

**CURRENT KNOWLEDGE:**

- Acute onset AIH can rapidly progress and requires urgent care
- Acute complications in AILD, e.g. obstructive jaundice and severe cholangitis in PSC, GI bleeding, are associated with high short-term mortality.

**LIVER CLINIC:**

- Organize an independent flow for urgent access to the hospital; if possible, use separate ER access
- Avoid endoscopy if possible, follow local protocols if needed
- Start steroids at the usual dose for treatment and Coordinate with the Transplant Center
- in case of infection be timely in tapering steroids and immunosop.

**PATIENTS:**

- In case of jaundice, bleeding or ascites contact the Local Emergency Number and your hepatologist
- Strictly respect isolation protocols
- Minimise the time any infected household spend in shared spaces
- Wash your hands often
- Strictly respect isolation protocols

**CURRENT KNOWLEDGE:**

- Decompensated cirrhotic patients (ascites, GI bleeding, hepatic encephalopathy, and jaundice) present a poor prognosis
- Decompensated patients require strict monitoring in order to avoid further complications

**LIVER CLINIC:**

- Postpone non-urgent medical visits until the emergency is over
- Organize an independent flow for urgent procedures (i.e. paracentesis); if possible, use separate (COVID-free) facility or home care
- Monitor your patients using a web-based system

**PATIENTS:**

- Wash your hands often
- Strictly respect isolation protocols
- Minimise the time any infected household spend in shared spaces
- Continue immunosuppressive drugs in unchanged doses
- Contact your GP in case of any symptoms
- Monitor weight and urinary quantity and keep a diary

General Practitioner (GP), European Reference Network (ERN), Autoimmune Liver Diseases (AILD), Autoimmune Hepatitis (AIH), Primary Sclerosing Cholangitis (PSC), Gastrointestinal (GI), Emergency Room (ER)

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