Challenges in the Management of patients with systemic light chain (AL) amyloidosis during the COVID-19 pandemic

Efstathios Kastritis¹, Ashutosh Wechalekar², Stefan Schönland³, Vaishali Sanchorawala⁴, Giampaolo Merlini⁵, Giovanni Palladini⁵, Monique Minnema⁶, Murielle Roussel⁷, Arnaud Jaccard⁸, Ute Hegenbart³, Shaji Kumar⁹, Maria Teresa Cibeira¹⁰, Joan Blade¹⁰, Meletios A. Dimopoulos¹

1. Plasma Cell Dyscrasia Unit, Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Greece
2. National Amyloidosis Centre, London, United Kingdom
3. Medical Department V, Amyloidosis Centre, University Hospital Heidelberg, Germany
4. Amyloidosis Center, Boston University School of Medicine and Boston Medical Center, Boston, USA

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bjh.16898

This article is protected by copyright. All rights reserved
5. Amyloidosis research and Treatment Center, Foundation “Istituto di Ricovery e Cura a Carattere Scientifico (IRCCS) Policlinico San Matteo” and Department of Molecular Medicine, University of Pavia, Pavia, Italy.
6. Department of Hematology, UMC Utrecht Cancer Center, Utrecht, The Netherlands
7. Clinical Hematology, IUC Oncopole/ CHU Toulouse, Toulouse, France
8. CHU Poitiers, Poitiers, France
9. Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA
10. Hematology Department, Amyloidosis and Myeloma Unit, Hospital Clinic of Barcelona, University of Barcelona, IDIBAPS, Barcelona, Spain

Correspondence
E. Kastritis, MD
Plasma Cell Dyscrasia Unit, Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Greece
e-mail: ekastritis@med.uoa.gr, ekastritis@gmail.com

Abstract
The SARS-CoV-2-associated disease (COVID-19) is primarily manifested as a respiratory tract infection but may affect and cause complications from multiple organ systems (cardiovascular,
gastrointestinal, kidneys, hematopoietic and immune systems) while no proven specific therapy exists. The challenges associated with COVID-19 are even greater for patients with light chain (AL) amyloidosis, a rare multisystemic disease affecting the heart, kidneys, liver, gastrointestinal and nervous system. Patients with AL amyloidosis may need to receive chemotherapy, which probably increases infection risk. Management of COVID-19 may be particularly challenging in patients with AL amyloidosis who often present with cardiac dysfunction, nephrotic syndrome, neuropathy, low blood pressure and gastrointestinal symptoms. In addition, AL patients may be more susceptible to toxicities of drugs used to manage COVID-19. Access to health care may be difficult or limited, diagnosis of AL amyloidosis may be delayed with detrimental consequences, treatment administration may need modification. Both patients and treating physicians need to adapt in a new reality.

Introduction

A pandemic associated with a SARS-CoV2 infection has become major global challenge, causing a health care crisis even in regions with developed health care systems and access to advanced health technologies. A major shift of health care resources has been made towards the management of the pandemic. Mortality is higher among older people, morbidly obese individuals and those with comorbidities, but younger people without major underlying diseases may also develop severe disease(Madjid, et al 2020, Tang, et al 2020). Challenges associated with COVID-19 are greater for patients with chronic conditions: they are considered more vulnerable to the infection while still need access to health care for the treatment of their underlying condition, in a situation of restricted resources. In addition, visiting hospitals may increase the risk of infection. Patients with malignancies were at increased risk, more likely to be diagnosed with COVID-19 and had a higher incidence of severe complications(Liang, et al 2020, Yu, et al 2020, Zhang, et al 2020b), while in some studies recent cancer treatment further increased this risk, but not in others(Robilotti, et al 2020).

Patients with light chain (AL) amyloidosis have an underlying usually low-grade plasma or B-cell malignancy causing their disease, and they receive chemotherapy(Merlini, et al 2018), thus, being at higher risk for infections(Kristinsson, et al 2012), including from SARS-CoV-2, and probably at higher risk for severe COVID-19(Pietrantonio and Garassino 2020). AL amyloidosis is a rare and challenging disease and the challenges may be even greater because special situations
may go unnoticed or unattended amid the pandemic. It is difficult to gather data for the management of the infection, design specific interventions and predict the special challenges in the management of patients with AL, who suffer a multisystemic disease and are facing an infection with multiorgan complications. Finally, there is a perception in the medical community in general about the futility of treatment in advanced amyloidosis, a fallacy that remains persistent in the era of modern treatments, leading to difficulties in decision making for patients who become unwell with COVID-19. The International Society of Amyloidosis (ISA) has issued a short guidance for patients with amyloidosis during the pandemic and called for data collection (2020). In this review we attempt to describe potential challenges associated with the management of patients with AL amyloidosis during the SARS-CoV2 pandemic.

**The SARS-CoV-2 infection**

SARS-CoV-2 invades the host human cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor followed by viral spike protein priming by host cell proteases including TMPRSS2 (Lu, et al 2020). SARS-CoV-2 primarily affects tissues expressing high levels of ACE2, including the lungs, the heart, the GI and the kidneys (Pan, et al 2020). COVID-19 is primarily manifested as a respiratory tract infection but affects multiple systems including the cardiovascular, gastrointestinal (GI), kidneys, hematopoietic and immune (Driggin, et al 2020, Mehta, et al 2020). In some patients, about 5 to 14 days from the onset of the first symptoms, a surge of clinical manifestations occurs with a pronounced systemic syndrome due to increase of inflammatory mediators and cytokines, characterized as “cytokine storm” (Huang, et al 2020, Li, et al 2020, Mehta, et al 2020). This can be associated with microvascular thrombosis of the lung and other vital organs (Ciceri, et al 2020). Given the spread of the virus in multiple organs and the cytokines which cause a deregulation in tissue homeostasis, this disease may become rapidly fatal.

**Special challenges for patients with AL amyloidosis**

The diagnosis of amyloidosis requires an increased index of clinical suspicion in the setting of multisystemic disease. Given the non-specific nature of most symptoms, the diagnosis is often missed or delayed (Lousada, et al 2015). Some tests (including imaging, cardiac and renal biomarkers) can increase or set the suspicion of the disease, but the correct diagnosis depends on tests (biopsies, typing, genetic testing) that require expertise, and which may not be widely available (Merlini, et al 2018). In the context of current pandemic many of the required resources
(health personnel or imaging facilities) may not be available, be overwhelmed (Emanuel, et al 2020, Moghadas, et al 2020) or be difficult to get access to, leading to significant delays in establishing correct diagnosis. In addition, there is a real risk that patients with less severe symptoms may defer to seek medical advice/care due to the fear of COVID-19, resulting in additional delays.

Patients with AL amyloidosis have multisystemic involvement, with different degrees of organ dysfunction and the clinical presentation in case of COVID-19 infection may be more severe, while patterns of COVID-19 evolution may differ from other patients. In addition, therapeutic approaches for COVID-19 may be associated with special challenges. Table 1 presents the systems involved in AL amyloidosis and COVID-19, depicting the complexity of a potential infection in AL patients.

Most patients with AL have cardiac dysfunction of various degrees. Patients with COVID-19 and preexisting cardiovascular disease are at increased risk of severe complications and death (Driggin, et al 2020, Guo, et al 2020, Shi, et al 2020). In addition, COVID-19 has been associated with cardiovascular complications (Chen, et al 2020c, Driggin, et al 2020, Guo, et al 2020, Shi, et al 2020). Patients with AL and heart involvement have a limited reserve to cope with COVID-19 associated cytokine storm, due to autonomic nervous system involvement, heart failure with low cardiac output (Stamatelopoulos, et al 2019, Wechalekar, et al 2013), low albumin due to nephrotic syndrome which further enhances extravascular leak, all of which reduce the effectiveness of vasoconstrictors (Stamatelopoulos, et al 2019). Patients with AL have a continuous loss of myocardial cells, as reflected by elevated troponin levels and pathology studies (Brenner, et al 2004). COVID-19 has also been associated with myocardial injury (Zhou, et al 2020), including cases of fulminant myocarditis with cardiogenic shock, as well as associated atrial and ventricular arrhythmias (Driggin, et al 2020, Hu, et al 2020). Hypoxia and electrolyte abnormalities are common in severe cases and further increase cardiac arrhythmia risk. There is limited data to understand these specific risks in the general COVID-19 infected population, even less in infected patients with AL amyloidosis. Monitoring of troponins may be useful but the rise due to COVID-19 myocarditis, in patients with AL amyloidosis needs to be interpreted in context of baseline levels which may already be increased. Most patients with AL amyloidosis are also receiving diuretics, placing them at increased risk of electrolyte imbalances, which may further trigger arrhythmias. The potential role of monitoring for arrhythmias (e.g. with telemetry) or

This article is protected by copyright. All rights reserved
additional pharmacologic therapies or interventions (such as implantable cardioverter defibrillator) is unknown. Given the poor tolerability of standard therapies for heart failure, such as beta-blockers and ACE inhibitors in patients with AL amyloidosis (Maurer, et al 2017), the management of arrhythmias during COVID-19 infection may be particularly difficult. The use of ACE inhibitors or angiotensin-receptor blockers is limited in amyloidosis patients due to poor tolerance, but data do not support their discontinuation specifically for COVID-19 (Hanff, et al 2020, Vaduganathan, et al 2020).

Therapies under investigation for COVID-19 have been associated with cardiovascular side effects (Driggin, et al 2020). Hydroxychloroquine (Gautret, et al 2020, Perinel, et al 2020, Yazdany and Kim 2020) with or without azithromycin (Gautret, et al 2020) is used in many centers despite the lack of strong data, but this therapy has been associated with QT prolongation, increasing the risk of drug-induced *torsades de pointes* and drug induced-sudden cardiac death (Juurlink 2020, Mehra, et al 2020). This risk can be further amplified if multiple medications which prolong QTc (i.e. azithromycin, lopinavir/ritonavir) are combined. For the general population which needs to be assessed for the risk of QTc prolongation and further management, there is some guidance (Giudicessi, et al). Baseline QTc status should be obtained and if exceeding 480 ms, in the absence of any drugs or factors prolonging QTc, may identify individuals at increased risk for QT-related ventricular arrhythmias. Patients with a resting QTc $\geq$ 500 ms, due to any cause (drugs, electrolyte abnormalities etc) have a greater risk for drug-induced arrhythmias; in such patients every effort should be made to correct electrolyte abnormalities (hypocalcemia, hypokalemia and hypomagnesemia), and re-evaluate non-essential medication causing QTc-prolongation. Closer monitoring should be considered, in the context of availability of such devices, staff and equipment protection and resources. The decision to start anti-COVID-19 therapy should depend on the risk-benefit ratio in each individual patient, but due to lack of data, clinical judgment is critical. Tocilizumab has been used in patients with COVID-19 during cytokine storm phase, with some encouraging results (Luo, et al 2020, Zhang, et al 2020c). It blocks IL-6 receptor, a key cytokine during this phase of the disease, however, several more cytokines are critical. Tocilizumab has proven safety profile during cytokine storm syndromes encountered in CAR-T cell therapy (Kotch, et al 2019) and has similar cardiovascular risk to other anti-rheumatic agents (Giles, et al 2020). The risk of secondary bacterial and other opportunistic infections with tocilizumab in patients already on immunosuppressive chemotherapy remains unclear.
Remdesivir has been evaluated in three studies ((Beigel, et al 2020, Grein, et al 2020, Wang, et al 2020b)) and may be of some benefit in patients with moderate or severe COVID-19. In the placebo-controlled studies severe toxicities were similar to placebo. Severe cardiac complications were uncommon and similar between groups. Most common complications included acute kidney injury, fever and increased aminotransferase levels. Remdesivir is given IV in a total volume of up to 250 mL, over 30 to 120 minutes, as a 200-mg loading dose on day 1, followed by a 100-mg maintenance dose for up to 10 days. Remdesivir in the treatment of COVID-19 is still under investigation, although its compassionate use has been approved. Remdesivir should be considered for patients with AL and COVID-19 as in any other patient with the infection, with close follow up for potential cardiorenal and liver toxicity.

Patients with renal involvement due to AL amyloidosis lose large amounts of albumin in urine, leading to low osmotic pressure, low intravascular volume, low blood pressure, peripheral edema and effusions, and are at increased risk of thromboembolic complications(Bever, et al 2016, Kastritis, et al 2017, Palladini, et al 2014, Sidana, et al 2019). Often, they have hypogammaglobulinemia due to urine loses of gamma-globulins further contributing to immune-compromised status while mounting an immune response may be inadequate. Beyond susceptibility to COVID-19, these patients may be more vulnerable to severe complications. It is more challenging to maintain intravascular volume and vascular tone in case of cytokine storm, and they are at risk for acute renal failure. Acute kidney injury common among patients with severe COVID-19, ranging from 0.5%(Guan, et al 2020) up to 25%(Chen, et al 2020c). Data from China showed that 43.9% of SARS-CoV-2-infected patients, especially those with AKI, developed proteinuria(Cheng, et al 2020) while SARS-CoV-2 could be detected in the urine of patients with severe COVID-19(Guan, et al 2020). Single cell transcriptomic analysis of normal kidneys indicated that there is co-expression of ACE2 and TMPRSS genes in podocytes and proximal straight tubule cells(Pan, et al 2020), suggesting that kidney might be a target organ for SARS-CoV-2. Thus, the risk for renal complications in patients with AL increases: a combination of direct viral insult with pre-renal complications due to a compromised circulatory system and pre-existing renal dysfunction may lead rapidly to renal failure and may portend a poorer outlook for renal function recovery. Dosing of many drugs may need adjustments due to renal dysfunction, including antibiotics, anti-coagulation and COVID-19-specific therapy. Chloroquine
is excreted partly (up to 50%) by the kidneys; some acute effects in patients with severe renal dysfunction have been described (Thorogood, et al 2007), but in the short term is relatively safe. About 15% to 25% of hydroxychloroquine is cleared by the kidneys (Tett, et al 1993), which is not dialyzable (Jallouli, et al 2015) and is bound to plasma proteins (McLachlan, et al 1993); in nephrotic patients this may cause an additional challenge to predict efficacy and safety.

**Experience with remdesivir in patients with eGFR<30 ml/min is limited.** A significant proportion of patients with AL amyloidosis require chronic dialysis, due to ESRD; these patients have significantly worse outcome than patients on dialysis for other indications (Leung, et al 2016). Renal transplantation is increasingly used for the management of ESRD in patients with AL amyloidosis (Angel-Korman, et al 2019). It may be preferable to defer planned organ transplantation due to increased risk immediately post-transplant with additional burden of immunosuppressive therapy. For patients with dialysis-dependent renal disease, measures to reduce the risk of COVID-19 in dialysis facilities should be followed (Kliger and Silberzweig 2020).

Patients with AL amyloidosis usually do not present with severe cytopenias, beyond those caused by chemotherapy. COVID-19 has been associated with certain hematologic complications (Terpos, et al 2020), the most common being lymphopenia, which may have prognostic implications. Coagulation disorders are frequent in severe COVID-19: elevated D-dimers and their increase are associated with poor prognosis (Han, et al 2020, Lillicrap 2020, Tang, et al 2020). Disseminated intravascular coagulation requires prompt intervention; other thrombotic complications have also been reported as the cause of death. Thromboprophylaxis is recommended for hospitalized patients with COVID-19 and may be associated with better outcome. The American Society of Hematology recommends that all hospitalized patients with COVID-19 should receive thromboprophylaxis with LMWH or fondaparinux (suggested over unfractionated heparin to reduce contact), unless the patient is at increased bleeding risk (Robilotti, et al 2020). However, in patients with AL amyloidosis the coagulation and fibrinolytic system may be already deregulated (Choufani, et al 2001, Kos, et al 2007, Pudusseri, et al 2019) while small vessels may be dysfunctional due to amyloid deposition (Migrino, et al 2011): a bleeding and a thrombotic diathesis co-exist. Thus, use of thromboprophylaxis in AL patients with COVID-19 should be cautious and closely monitored.
Gastrointestinal involvement is common in AL, presenting with diarrhea, constipation or alternating between the two, malabsorption, poor nutritional status and sarcopenia (Sattianayagam, et al 2013), further increasing susceptibility to infections. Diarrhea, a common symptom of COVID-19 was initially neglected; an incidence rate ranging from 2% to 50% of cases is reported (D’Amico, et al 2020). Importantly, it may precede or present along with the respiratory symptoms. SARS-CoV-2 binds to ACE2 and TMPRSS2 that are expressed in the small intestinal epithelia and viral RNA may shed in feces (Chen, et al 2020a, Chen, et al 2020d). A significant proportion of patients with AL amyloidosis of the GI suffers from chronic diarrhea, so this symptom may go unnoticed as initial presentation of COVID-19. The management of diarrhea is symptomatic and does not seem to be associated with severe complications per se. Liver involvement is common in AL, but the clinical manifestations are usually mild, including hepatomegaly and increased cholestatic enzymes; symptomatic involvement (rupture, portal hypertension, hepatic failure) is rare. Patients with COVID-19 may develop different degrees of liver dysfunction, with an incidence ranging between ~20% to 78% in severe cases. Patients mainly presented with abnormal levels of alanine aminotransferase and aspartate aminotransferase accompanied by slightly elevated bilirubin levels (Chen, et al 2020b, Guan, et al 2020, Huang, et al 2020). The mechanisms for hepatic injury in patients with COVID-19 may include direct damage to bile duct epithelial cells expressing ACE2 (Chai, et al 2020) and immune-mediated inflammation in severe COVID-19 (Zhang, et al 2020a). In patients with AL amyloidosis cholestasis predominates; it is unknown whether infection with SARS-CoV-2 can further deteriorate liver function.

Peripheral and autonomic neuropathy are common in AL and may be of different types (Kokotis, et al 2020). There is limited data for neurologic manifestations among patients with COVID-19. In a retrospective series from China, 36.4% of the patients had neurologic manifestations, mostly in those with severe infection, and included acute cerebrovascular diseases, impaired consciousness and rhabdomyolysis; 8.9% had peripheral nervous symptoms, most common being taste and smell impairment (Helms, et al 2020, Mao, et al 2020). The risk of cerebrovascular complications seems to be increased in patients with COVID-19, as they are also increased in patients with AL amyloidosis, especially those with cardiac involvement.

**Treatment of AL amyloidosis during the COVID-19 pandemic**

This article is protected by copyright. All rights reserved
The therapeutic approach to a patient with AL amyloidosis is individualized based on risk assessment (Merlini, et al 2018, Wechalekar, et al 2016), aiming to a rapid and sustained reduction and ultimately elimination of free light chains (FLCs), with limited risk of toxicity, by means of cytotoxic therapy targeting the plasma/B-cell clone. Additional adjustments to therapy may be required during COVID-19 pandemic. Chemotherapy causes immunosuppression, which varies for different agents and regimens. It has been hypothesized, that patients receiving immunosuppressors or immunomodulators might have a milder clinical presentation of COVID-19 (Mehta, et al 2020, Ritchie and Singanayagam 2020); however, clinical data remains limited. Recent data from immunosuppressed patients from Italy, appears to suggest no increased risk of severe infections (3 out of 700 children with liver transplants tested positive and none with severe disease) (D'Antiga 2020); however, in adult patients with renal transplants morbidity and mortality were high (Alberici, et al 2020). Bortezomib and other proteasome inhibitors (ixazomib, carfilzomib) are associated with increased risk of viral infections (such as varicella zoster virus reactivation, and perhaps cytomegalovirus) (Sharpley, et al 2020). Patients on bortezomib may also present with pulmonary infiltrates and fever due to hypersensitivity pneumonia (Balsman 2017, Zappasodi, et al 2007), and should be kept in the differential diagnosis when other infectious causes are excluded (including COVID-19). IMiDs are also associated with increased risk of pulmonary infections and thrombotic complications (Palumbo, et al 2008) as well as pneumonitis (Zagouri, et al 2011). Cyclophosphamide causes B- and T-cell depletion, bortezomib and steroids are associated with lymphopenia. Daratumumab depletes NK-cells, which are important for responses to viral infections, and has been associated with an increased risk of viral and respiratory tract infections (Kimmich, et al 2020, Roussel, et al 2020, Sanchorawala, et al 2020), in combination with other agents this risk may be even higher. Cytotoxic and/or immunomodulatory therapy in a patient with AL amyloidosis who has been infected with SARS-CoV-2 should be discontinued until recovery.

AL amyloidosis is a deadly disease; delays in the diagnosis and initiation of therapy may be detrimental. There is no “asymptomatic” AL amyloidosis and most patients are diagnosed due to symptoms and complications. Therapy should start upon confirmation of the diagnosis in almost all cases; very few will be asymptomatic and be diagnosed as part of monitoring for prior MGUS. Despite the pandemic, indications to start therapy should not change, especially in patients with heart involvement who are at increased risk of amyloidosis-related death, and which in most cases
exceeds the risk of acquiring COVID-19. It is not possible to define the optimal balance between the need for treatment for AL and the potential risk of infection. There is significant geographic variation in the severity of the pandemic and in some areas the risk of acquiring the infection is low, so that there may be no need for modifications of therapy.

In patients in good clinical status, without cardiac amyloidosis and with stable organ function, for example with isolated renal involvement, one must balance the risks of delayed therapy vs risk of infection, in the each phase of the pandemic. Patients with preserved organ function (low-grade proteinuria and preserved eGFR, low cardiac biomarkers) have the best chances to achieve a remission, improve organ function and avoid complications such as dialysis. However, a short delay for 4-6 weeks, until the pandemic is under control in the area and local health care system adjusts, may be without significant consequences. Patients in relapse are often more “stable” than newly diagnosed ones. In those with slow increase and relatively low levels of circulating FLCs, without heart involvement, the indications to start therapy are anyway unclear (Palladini and Merlini 2019, Sanchoarawala 2019): such patients could probably wait and avoid frequent hospital visits. Again, for patients with cardiac involvement delays to provide therapy should be cautiously considered (Palladini and Merlini 2019).

A common question that arises is whether the treatment should change to a regimen or schedule that reduces hospital visits. Many experts suggested that oral therapies may be used instead of intravenous (IV) or subcutaneous (SC) therapies given in the hospital, or change to regimens that require less frequent visits or even delaying or skipping doses (Banna, et al 2020, Hanna, et al 2020, Pietrantonio and Garassino 2020). These strategies are expected to reduce the exposure of vulnerable patients to hospital environment and other “risk” contacts, while they save resources. However, these strategies cannot be applied to all cancer patients and a potential risk/benefit assessment should be performed before deciding to change therapy or skip doses/visits. For patients with acute diseases, in which full therapy may be life-saving the treatment should probably not change. This is the case of newly diagnosed AL amyloidosis: a rapid disease control is required in most patients with the most effective and safe therapy and for some patients optimal anti-AL therapy should start even in the midst of the outbreak, for example for patients with cardiac involvement. Treatments for AL amyloidosis have not been developed in the context of multiple randomized studies, thus, we have limited data to propose one therapy over the other or assess the importance of full vs reduced dosing of critical drugs such as bortezomib or
A randomized study showed that the combination of SC/IV bortezomib with oral melphalan and dexamethasone (BMDex) is associated with faster and deeper response than oral MDex; thus, avoiding bortezomib to keep only MDex may be associated with inferior outcomes in patients with previously untreated AL amyloidosis (Kastritis, et al 2016). Minimizing unnecessary visits and delays may be feasible and safe without compromising efficacy. Using SC bortezomib requires minimal time in the infusion center and can be done on an outpatient setting; oral instead of IV cyclophosphamide has similar pharmacokinetics and efficacy (Mikhael, et al 2012, Struck, et al 1987). Although CyBorD/VCD and BMDex pose low risk of neutropenia (although higher for BMDex), CBC monitoring to reduce chemotherapy dose or provide prophylactic growth factors might be considered in selected patients. **In order to reduce time of infusion and avoid excessive fluid, daratumumab should be given at lower volumes (of 500 ml), also allowing infusion in reduced time (in 90 min).** This strategy can be employed after the first few infusions, provided that no major infusion-related reactions occurred (Barr, et al 2018). Given that daratumumab was given for a fixed duration in prospective studies (Palladini, et al 2020, Roussel, et al 2020, Sanchorawala, et al 2020) discontinuation may be considered in patients in complete response (CR) or after 2 years of therapy. **Due to the lack of direct comparison is difficult to propose substituting ixazomib for bortezomib, at least in previously untreated patients or those with severe cardiac involvement. However, ixazomib may be an option for some selected patients or be an alternative for those already on bortezomib who have achieved a response, in a heavily affected area.** In the relapsed setting, however, ixazomib-based therapy is a reasonable choice for patients with or without prior exposure to bortezomib (Dispenzieri, et al 2019). There are no data to support any dose modifications of any of the oral anti-plasma cell drugs during the pandemic.

For selected patients who have achieved a satisfactory hematologic response (for example CR or VGPR or even PR with organ response), the treating physician may discuss to complete therapy earlier or continue with a less intensive schedule (for example reduce weekly to bi-weekly bortezomib). Steroid dose can be reduced or discontinued in patients on long term lenalidomide, supported by data in myeloma (Larocca, et al 2018). If HDM/ASCT is planned, delaying or deferring the transplant may be a safer approach (Terpos, et al 2020). HDM/ASCT requires hospitalization, may require intensive care for management of complications in some patients,
blood and platelet transfusions and causes severe immunosuppression. In addition, there is no randomized data to support superiority of transplant over modern conventional-dose therapies in patients with AL amyloidosis; deferring transplant may also be an option (Manwani, et al 2018, Trachtenberg, et al 2019).

Enrollment in clinical trials has been affected by the pandemics, some have temporarily hold enrolment or modified visit schedule to essential ones, without compromising patient safety and data integrity. However, clinical trials are critical for the development of new therapies for AL amyloidosis and patients should be encouraged to participate.

Following the patients with AL amyloidosis remotely

Hospital visits should be reduced to those necessary, thus, depending on specific local conditions and standards, local laboratories may be used to follow blood and urine parameters, as in other hematologic malignancies (Willan, et al 2020). Shipping tissue samples to referral centers for typing can reduce the need for traveling. Blood samples for measurement of FLCs, NTproBNP or troponin levels are rather stable if shipped overnight. Specialized testing can be usually postponed for patients in hematologic remission and stable condition and reserved for those in which a major treatment decision needs to be made. Home collection of blood samples could be used, if this service is available, with appropriate social distancing measures; in our practice this has been an option that many patients accept. Simple measures like home measurement of weight, pulse rate and blood pressure can allow for meaningful discussion for management of heart failure in these patients. Telemedicine may be helpful, but one needs to take into consideration certain limitations of the distant physician-patient contact; in a rare and complex disease such as AL amyloidosis direct assessment from specialized experienced physicians may be critical.

Prophylactic measures for patients with AL amyloidosis during the pandemic

There is no vaccine or drug to use as prophylaxis for COVID-19. The most effective prophylactic measure is social distancing, isolation of those at risk for severe complications, and strict hygiene rules to reduce the virus transmission rate. There are no specific measures that patients with AL amyloidosis should follow to prevent COVID-19. Vaccination against influenza and Pneumococcus should be continued, since these two diseases are common and may be lethal. There is no data to support screening for COVID-19 in patients with malignancies, including with
AL amyloidosis. Local guidelines should be followed; however, the threshold to test a patient with AL in case of suspicion of COVID-19 should be low, due to the potential risk of rapid clinical deterioration in those with multisystemic amyloidotic involvement. PCR testing is the current standard for the diagnosis of acute infection (Wang, et al 2020a). It is expected that valid serological tests will become available, that will detect specific antibodies to SARS-CoV-2 allowing to detect past or relatively recent infection; however, there is no data regarding the immune status against the virus based on these tests. If a vaccine becomes available, patients with AL amyloidosis should be considered for vaccination, as with other standard vaccines, taking into account its safety and efficacy. Whether patients on daratumumab, bortezomib or rituximab will mount an immune response to the virus, or develop an adequate immune response to vaccination, is unknown and should be prospectively studied.

Many patients with AL amyloidosis are already on antivirals (acyclovir, valacyclovir etc) as prophylaxis due to therapy with proteasome inhibitors or daratumumab, but, have no activity against SARS-CoV-2. Prophylactic antibiotics are often given either for prophylaxis (such as quinolone antibiotics (Drayson, et al 2019)) or for their potential anti-fibril activity (doxycycline (Wechalekar and Whelan 2017)). These drugs have no effect on COVID-19, but may reduce the risk of other infections and in the current context should probably be continued. In patients with AL presenting with fever and symptoms of respiratory infection, especially if are tested negative for COVID-19, there is still a significant risk of a bacterial or other viral (such as influenza) infection, which should not be overlooked. There is limited data to support the use of prophylactic immunoglobulins outside the context of severe hypogammaglobulinemia with repeated infections. SARS-CoV2 is a new virus and there is no population immunity and anti-SARS-CoV2 antibodies are not expected to exist in immunoglobulin products. Convalescent plasma from previously infected COVID-19 patients and recovered donors could offer passive immunity in some selected patients and is under investigation.

Access to health care for AL patients developing SARS-CoV2 infection

Most health care systems have made major adjustments to routine patient care to allow for high influx of patients presenting with COVID-19 infection. The access to monitored beds and intensive care units may be limited. The outcomes of patients with significant multiorgan damage on ICUs is poor. In the current climate, where every ICU bed has become a precious resource, the best utilization for patients with multiorgan AL amyloidosis and severe COVID-19 infection

This article is protected by copyright. All rights reserved
remain unknown. In each case, the care must be individualized – a renal AL patient with good potential long term outcome should be a good case for full care. Early discussion about resuscitation status with the patient and family with realistic assessments of outcomes is important to avoid difficult decisions when patients are admitted with COVID-19 and may not have access to supportive family.

Conclusions
COVID-19 is an ongoing pandemic with data changing continuously, and new information acquired with a speed never seen before. Still, prospective data are scarce. For patients with a rare disease such as AL amyloidosis, is even more difficult to collect information on a large scale and make informed decisions. Ongoing data collection, observations and single case reports are all critical since it is expected that the end of the pandemic is not close. At this date more than 600 clinical trial are registered in clinicaltrials.gov for COVID-19. Since there is limited data for this disease, we urge to enroll patients in clinical trials. The ISA drives an initiative to collect data of amyloidosis patients with COVID-19; ASH is also gathering data for patients with hematologic diseases and COVID-19, including patients with AL amyloidosis.

Given the multisystemic involvement, the use of chemoimmunotherapy and the age of most of our patients, it is essential to consider patients with AL amyloidosis as an extremely vulnerable population, with limited reserves to fight COVID-19. As we accumulate data, we will be able to provide better care to our patients, perhaps with more specific and safe therapies for the infection. All patients with systemic AL amyloidosis should be informed of their vulnerability and encouraged to adhere to measures to prevent infection. We should assure our patients with AL amyloidosis that we will continue our efforts to provide optimal care, even during this period of shortages and limited health care resources.

Acknowledgments: this manuscript was an International Society of Amyloidosis effort

Author contributions: EK prepared the first draft, AW, SS, VS, GM, GP, MM, MR, AJ, UH, SK, MTC, JB, MAD reviewed and made substantial changes and additions in the manuscript and provided their expert opinion

Conflicts of interest:
E.K: received honoraria for educational lectures and participated in advisory boards from Amgen, Genesis Pharma, Janssen, Takeda, and received research support from Janssen and Amgen.

VS – Research funding to the institution: Celgene, Prothena, Takeda, Janssen, Scientific advisory board: Proclara, CaleumS.O.S. - Research funding to the institution: Prothena, Janssen, Sanofi. Scientific advisory board: Caleum, Prothena, Janssen, Sanofi and Takeda. Honoraria for educational lectures from Janssen and Takeda. Travel grants from Janssen, Takeda and Medac.

UH: has received travel grants from Janssen, Prothena and Pfizer, served on the advisory boards for Pfizer and Prothena, and has received honoraria from Janssen, Pfizer, Alnylam and Akcea.

JB has received honoraria for lectures and advisory boards from Janssen, Celgene, Amgen, Takeda and Oncopeptides.

M.T.C. received honoraria for educational lectures from Janssen, Celgene and Amgen, and advisory boards from Janssen and Akcea.

MR: research funding, travel fees and accommodation from Janssen

MAD: received honoraria/personal fees from Amgen, BMS, Celgene, GSK, Janssen, Takeda.

SoS: has received research funding from Janssen and Sanofi and travel grants from Janssen, Prothena, Takeda and Medac, served on the advisory boards for Janssen, Takeda and Prothena, and has received honoraria from Janssen, Takeda, Prothena.

MCM: honoraria to institution Amgen, Janssen, Servier, Gilead. Takeda, BMS. Research funding to institution: Celgene, Travel grants Amgen, Celgene

References
(2020).
Alberici, F., Delbarba, E., Manenti, C., Econimo, L., Valerio, F., Pola, A., Maffei, C., Possenti, S., Piva, S., Latronico, N., Foca, E., Castelli, F., Gaggia, P., Movilli, E., Bove, S., Malberti, F., Farina, M., Bracchi, M., Costantino, E.M., Bossini, N., Gaggiotti, M., Scolari, F. & Brescia Renal, C.T.F. (2020) Management Of Patients On Dialysis And With Kidney Transplant During SARS-COV-2 (COVID-19) Pandemic In Brescia, Italy. *Kidney Int Rep.*

Angel-Korman, A., Stern, L., Sarosiek, S., Sloan, J.M., Doros, G., Sanchorawala, V. & Havasi, A. (2019) Long-term outcome of kidney transplantation in AL amyloidosis. *Kidney International, 95*, 405-411.
Balsman, E. (2017) Bortezomib therapy-related lung disease in a patient with light chain amyloidosis: A case report. J Oncol Pharm Pract, 23, 545-548.

Banna, G., Curioni-Fontecedro, A., Friedlaender, A. & Addeo, A. (2020) How we treat patients with lung cancer during the SARS-CoV-2 pandemic: primum non nocere. ESMO Open, 5.

Barr, H., Dempsey, J., Waller, A., Huang, Y., Williams, N., Sharma, N., Benson, D.M., Rosko, A.E., Efebera, Y.A. & Hofmeister, C.C. (2018) Ninety-minute daratumumab infusion is safe in multiple myeloma. Leukemia, 32, 2495-2518.

Beigel, J.H., Tomashek, K.M., Dodd, L.E., Mehta, A.K., Zingman, B.S., Kalil, A.C., Hohmann, E., Chu, H.Y., Luetkemeyer, A., Kline, S., Lopez de Castilla, D., Finberg, R.W., Dierberg, K., Tapson, V., Hsieh, L., Patterson, T.F., Paredes, R., Sweeney, D.A., Short, W.R., Touloumi, G., Lye, D.C., Ohmagari, N., Oh, M.D., Ruiz-Palacios, G.M., Benfield, T., Fatkenheuer, G., Kortepeter, M.G., Atmar, R.L., Creech, C.B., Lundgren, J., Babiker, A.G., Pett, S., Neaton, J.D., Burgess, T.H., Bonnett, T., Green, M., Makowski, M., Osinusi, A., Nayak, S., Lane, H.C. & Members, A.-S.G. (2020) Remdesivir for the Treatment of Covid-19 - Preliminary Report. N Engl J Med.

Bever, K.M., Masha, L.I., Sun, F., Stern, L., Havasi, A., Berk, J.L., Sanchorawala, V., Seldin, D.C. & Sloan, J.M. (2016) Risk factors for venous thromboembolism in immunoglobulin light chain amyloidosis. Haematologica, 101, 86-90.

Brenner, D.A., Jain, M., Pimentel, D.R., Wang, B., Connors, L.H., Skinner, M., Apstein, C.S. & Liao, R. (2004) Human amyloidogenic light chains directly impair cardiomyocyte function through an increase in cellular oxidant stress. Circulation Research, 94, 1008-1010.

Chai, X., Hu, L., Zhang, Y., Han, W., Lu, Z., Ke, A., Zhou, J., Shi, G., Fang, N., Fan, J., Cai, J., Fan, J. & Lan, F. (2020) Specific ACE2 Expression in Cholangiocytes May Cause Liver Damage After 2019-nCoV Infection. bioRxiv, 2020.2002.2003.931766.

Chen, C., Gao, G., Xu, Y., Pu, L., Wang, Q., Wang, L., Wang, W., Song, Y., Chen, M., Wang, L., Yu, F., Yang, S., Tang, Y., Zhao, L., Wang, H., Wang, Y., Zeng, H. & Zhang, F. (2020a) SARS-CoV-2-Positive Sputum and Feces After Conversion of Pharyngeal Samples in Patients With COVID-19. Ann Intern Med.

Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., Qiu, Y., Wang, J., Liu, Y., Wei, Y., Xia, J., Yu, T., Zhang, X. & Zhang, L. (2020b) Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet, 395, 507-513.

Chen, T., Wu, D., Chen, H., Yan, W., Yang, D., Chen, G., Ma, K., Xu, D., Yu, H., Wang, H., Wang, T., Guo, W., Chen, J., Ding, C., Zhang, X., Huang, J., Han, M., Li, S., Luo, X., Zhao, J. & Ning, Q. (2020c) Clinical...
characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ, 368, m1091.

Chen, Y., Chen, L., Deng, Q., Zhang, G., Wu, K., Ni, L., Yang, Y., Liu, B., Wang, W., Wei, C., Yang, J., Ye, G. & Cheng, Z. (2020d) The Presence of SARS-CoV-2 RNA in Feces of COVID-19 Patients. J Med Virol.

Cheng, Y., Luo, R., Wang, K., Zhang, M., Wang, Z., Dong, L., Li, J., Yao, Y., Ge, S. & Xu, G. (2020) Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int.

Choufani, E.B., Sanchorawala, V., Ernst, T., Quillen, K., Skinner, M., Wright, D.G. & Seldin, D.C. (2001) Acquired factor X deficiency in patients with amyloid light-chain amyloidosis: incidence, bleeding manifestations, and response to high-dose chemotherapy. Blood, 97, 1885-1887.

Ciceri, F., Beretta, L., Scandroglio, A.M., Colombo, S., Landoni, G., Ruggeri, A., Peccatori, J., D’Angelo, A., De Cobelli, F., Rovere-Querini, P., Tresoldi, M., Dagna, L. & Zangrillo, A. (2020) Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): an atypical acute respiratory distress syndrome working hypothesis. Crit Care Resusc.

D’Amico, F., Baumgart, D.C., Danese, S. & Peyrin-Biroulet, L. (2020) Diarrhea during COVID-19 infection: pathogenesis, epidemiology, prevention and management. Clin Gastroenterol Hepatol.

D’Antiga, L. (2020) Coronaviruses and immunosuppressed patients. The facts during the third epidemic. Liver Transpl.

Dispenzieri, A., Kastritis, E., Wechalekar, A. & al, e. (2019) Primary results from the phase 3 tourmaline-AL1 trial of ixazomib-dexamethasone versus physician’s choice of therapy in patients (Pts) with relapsed/refractory primary systemic AL amyloidosis (RRAL). Blood, 134, 139.

Drayson, M.T., Bowcock, S., Planche, T., Iqbal, G., Pratt, G., Yong, K., Wood, J., Raynes, K., Higgins, H., Dawkins, B., Meads, D., Hulme, C.T., Monahan, I., Karunanithi, K., Dignum, H., Belsham, E., Neilson, J., Harrison, B., Lokare, A., Campbell, G., Hamblin, M., Hawkey, P., Whittaker, A.C., Low, E., Dunn, J.A., Group, T.T.M. & Trial, I. (2019) Levofloxacin prophylaxis in patients with newly diagnosed myeloma (TEAMM): a multicentre, double-blind, placebo-controlled, randomised, phase 3 trial. Lancet Oncol, 20, 1760-1772.

Driggin, E., Madhavan, M.V., Bikdeli, B., Chuich, T., Laracy, J., Bondi-Zoccai, G., Brown, T.S., Nigoghossian, C., Zidar, D.A., Haythe, J., Brodie, D., Beckman, J.A., Kirtane, A.J., Stone, G.W., Krumholz, H.M. & Parikh, S.A. (2020) Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the Coronavirus Disease 2019 (COVID-19) Pandemic. J Am Coll Cardiol.

Emanuel, E.J., Persad, G., Upshur, R., Thome, B., Parker, M., Glickman, A., Zhang, C., Boyle, C., Smith, M. & Phillips, J.P. (2020) Fair Allocation of Scarce Medical Resources in the Time of Covid-19. New England Journal of Medicine.
Gautret, P., Lagier, J.C., Parola, P., Hoang, V.T., Meddeb, L., Mailhe, M., Doudier, B., Courjon, J.,
Giordanengo, V., Vieira, V.E., Dupont, H.T., Honore, S., Colson, P., Chabriere, E., La Scola, B.,
Rolain, J.M., Brouqui, P. & Raoult, D. (2020) Hydroxychloroquine and azithromycin as a treatment
of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*,
105949.

Giles, J.T., Sattar, N., Gabriel, S., Ridker, P.M., Gay, S., Warne, C., Musselman, D., Brockwell, L., Shittu, E.,
Klearman, M. & Fleming, T.R. (2020) Cardiovascular Safety of Tocilizumab Versus Etanercept in
Rheumatoid Arthritis: A Randomized Controlled Trial. *Arthritis Rheumatol.*, 72, 31-40.

Giudicessi, J.R., Noseworthy, P.A., Friedman, P.A. & Ackerman, M.J. Urgent Guidance for Navigating and
Circumventing the QTc-Prolonging and Torsadogenic Potential of Possible Pharmacotherapies for
Coronavirus Disease 19 (COVID-19). *Mayo Clinic Proceedings*.

Grein, J., Ohmagari, N., Shin, D., Diaz, G., Asperges, E., Castagna, A., Feldt, T., Green, G., Green, M.L.,
Lescure, F.X., Nicolet, E., Oda, R., Yo, K., Quiros-Roldan, E., Studemeister, A., Redinski, J., Ahmed,
S., Bernett, J., Chelliah, D., Chen, D., Chihara, S., Cohen, S.H., Cunningham, J., D’Arminio Monforte,
A., Ismail, S., Kato, H., Lapadula, G., L’Her, E., Maeno, T., Majumder, S., Massari, M., Mora-Rillo,
M., Mutoh, Y., Nguyen, D., Verweij, E., Zoufaly, A., Osinusi, A.O., DeZure, A., Zhao, Y., Zhong, L.,
Chokkalingam, A., Elboudwarej, E., Telep, L., Timbs, L., Henne, I., Sellers, S., Cao, H., Tan, S.K.,
Winterbourne, L., Desai, P., Mera, R., Gaggar, A., Myers, R.P., Brainard, D.M., Childs, R. & Flanigan,
T. (2020) Compassionate Use of Remdesivir for Patients with Severe Covid-19. *N Engl J Med*.

Guan, W.J., Ni, Z.Y., Hu, Y., Liang, W.H., Ou, C.Q., He, J.X., Liu, L., Shan, H., Lei, C.L., Hui, D.S.C., Du, B., Li,
L.J., Zeng, G., Yuen, K.Y., Chen, R.C., Tang, C.L., Wang, T., Chen, P.Y., Xiang, J., Li, S.Y., Wang, J.L.,
Liang, Z.J., Peng, Y.X., Wei, L., Liu, Y., Hu, Y.H., Peng, P., Wang, J.M., Liu, J.Y., Chen, Z., Li, G., Zheng,
Z.J., Qiu, S.Q., Luo, J., Ye, C.J., Zhu, S.Y., Zhong, N.S. & China Medical Treatment Expert Group for,
C. (2020) Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*.

Guo, T., Fan, Y., Chen, M., Wu, X., Zhang, L., He, T., Wang, H., Wan, J., Wang, X. & Lu, Z. (2020)
Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-
19). *JAMA Cardiol*.

Han, H., Yang, L., Liu, R., Liu, F., Wu, K.L., Li, J., Liu, X.H. & Zhu, C.L. (2020) Prominent changes in blood
coagulation of patients with SARS-CoV-2 infection. *Clin Chem Lab Med*.

Hanff, T.C., Harhay, M.O., Brown, T.S., Cohen, J.B. & Mohareb, A.M. (2020) Is There an Association
Between COVID-19 Mortality and the Renin-Angiotensin System-a Call for Epidemiologic
Investigations. *Clin Infect Dis*. 

This article is protected by copyright. All rights reserved
Hanna, T.P., Evans, G.A. & Booth, C.M. (2020) Cancer, COVID-19 and the precautionary principle: prioritizing treatment during a global pandemic. *Nat Rev Clin Oncol.*

Helms, J., Kremer, S., Merdji, H., Clere-Jehl, R., Schenck, M., Kummerlen, C., Collange, O., Boulay, C., Fafi-Kremer, S., Ohana, M., Anheim, M. & Meziani, F. (2020) Neurologic Features in Severe SARS-CoV-2 Infection. *New England Journal of Medicine.*

Hu, H., Ma, F., Wei, X. & Fang, Y. (2020) Coronavirus fulminant myocarditis saved with glucocorticoid and human immunoglobulin. *Eur Heart J.*

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z., Yu, T., Xia, J., Wei, Y., Wu, W., Xie, X., Yin, W., Li, H., Liu, M., Xiao, Y., Gao, H., Guo, L., Xie, J., Wang, G., Jiang, R., Gao, Z., Jin, Q., Wang, J. & Cao, B. (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet,* 395, 497-506.

Jallouli, M., Galicier, L., Zahr, N., Aumaitre, O., Frances, C., Le Guern, V., Liote, F., Smail, A., Limal, N., Perard, L., Desmurs-Clavel, H., Le Thi Huong, D., Asli, B., Kahn, J.E., Pourrat, J., Sailler, L., Ackermann, F., Papo, T., Sacre, K., Fain, O., Stirnemann, J., Cacoub, P., Leroux, G., Cohen-Bittan, J., Sellam, J., Mariette, X., Blanchet, B., Hulot, J.S., Amoura, Z., Piette, J.C., Costedoat-Chalumeau, N. & Plaquenil Lupus Systemic Study, G. (2015) Determinants of hydroxychloroquine blood concentration variations in systemic lupus erythematosus. *Arthritis Rheumatol,* 67, 2176-2184.

Juurlink, D.N. (2020) Safety considerations with chloroquine, hydroxychloroquine and azithromycin in the management of SARS-CoV-2 infection. *CMAJ.*

Kastritis, E., Gavriatopoulou, M., Roussou, M., Migkou, M., Fotiou, D., Ziogas, D.C., Kanellias, N., Eleutherakis-Papaioakouvou, E., Panagiotidis, I., Giannouli, S., Psimou, E., Marinaki, S., Apostolou, T., Gakiopoulou, H., Tasidou, A., Papassotiriou, I., Terpos, E. & Dimopoulos, M.A. (2017) Renal outcomes in patients with AL amyloidosis: Prognostic factors, renal response and the impact of therapy. *American Journal of Hematology,* 92, 632-639.

Kastritis, E., Leleu, X., Arnulf, B., Zamagni, E., Cibeira, M.T., Kwok, F., Mollee, P., Hajek, R., Moreau, P., Jaccard, A., Schönland, S., Filshie, R., Nicolas-Virelizier, E., Augustson, B., Mateos, M.-V., Wechalekar, A., Hachulla, E., Milani, P., Dimopoulos, M.A., Ferrand, J.-P., Foli, A., Gavriatopoulou, M., Palumbo, A., Sonneveld, P., Johnsen, H.E., Merlini, G. & Palladini, G. (2016) A Randomized Phase III Trial of Melphalan and Dexamethasone (MDex) Versus Bortezomib, Melphalan and Dexamethasone (BMDex) for Untreated Patients with AL Amyloidosis. *Blood,* 128, 646-646.

Kimmich, C.R., Terzer, T., Benner, A., Dittrich, T., Veelken, K., Carpinteiro, A., Hansen, T., Goldschmidt, H., Seckinger, A., Hose, D., Jauch, A., Worner, S., Beimler, J., Muller-Tidow, C., Hegenbart, U. &
Schonland, S.O. (2020) Daratumumab for systemic AL amyloidosis: prognostic factors and adverse outcome with nephrotic range albuminuria. *Blood.*

Kligler, A.S. & Silberzweig, J. (2020) Mitigating Risk of COVID-19 in Dialysis Facilities. *Clin J Am Soc Nephrol.*

Kokotis, P., Manios, E., Schmelz, M., Fotiou, D., Dialoupi, I., Gavriatopoulou, M., Roussou, M., Lykka, A., Dimopoulos, M.A. & Kastritis, E. (2020) Involvement of small nerve fibres and autonomic nervous system in AL amyloidosis: comprehensive characteristics and clinical implications. *Amyloid,* 1-8.

Kos, C.A., Ward, J.E., Malek, K., Sanchorawala, V., Wright, D.G., O’Hara, C., Connors, L., Skinner, M. & Seldin, D.C. (2007) Association of acquired von Willebrand syndrome with AL amyloidosis. *American Journal of Hematology,* 82, 363-367.

Kotch, C., Barrett, D. & Teachey, D.T. (2019) Tocilizumab for the treatment of chimeric antigen receptor T cell-induced cytokine release syndrome. *Expert Rev Clin Immunol,* 15, 813-822.

Kristinsson, S.Y., Tang, M., Pfeiffer, R.M., Bjorkholm, M., Goldin, L.R., Blimark, C., Mellqvist, U.H., Wahlin, A., Turesson, I. & Landgren, O. (2012) Monoclonal gammopathy of undetermined significance and risk of infections: a population-based study. *Haematologica,* 97, 854-858.

Larocca, A., Salvini, M., De Paoli, L., Cascavilla, N., Benevolo, G., Galli, M., Montefusco, V., Caravita di Toritto, T., Baraldi, A., Spada, S., Giuliani, N., Pautasso, C., Pulini, S., Ronconi, S., Pescosta, N., Liberati, A.M., Patriarca, F., Cellini, C., Tosi, P., Offidani, M., Cavo, M., Palumbo, A., Boccadoro, M. & Bringhen, S. (2018) Efficacy and Feasibility of Dose/Schedule-Adjusted Rd-R Vs. Continuous Rd in Elderly and Intermediate-Fit Newly Diagnosed Multiple Myeloma (NDMM) Patients: RV-MM-PI-0752 Phase III Randomized Study. *Blood,* 132, 305-305.

Leung, N., Kumar, S.K., Glavey, S.V., Dispenzieri, A., Lacy, M.Q., Buadi, F.K., Hayman, S.R., Dingli, D., Kapoor, P., Zeldenrust, S.R., Russell, S.J., Lust, J.A., Hogan, W.J., Rajkumar, S.V., Gastineau, D.A., Kourelis, T.V., Lin, Y., Gonsalves, W.I., Go, R.S. & Gertz, M.A. (2016) The impact of dialysis on the survival of patients with immunoglobulin light chain (AL) amyloidosis undergoing autologous stem cell transplantation. *Nephrology Dialysis Transplantation,* 31, 1284-1289.

Li, T., Lu, H. & Zhang, W. (2020) Clinical observation and management of COVID-19 patients. *Emerg Microbes Infect,* 9, 687-690.

Liang, W., Guan, W., Chen, R., Wang, W., Li, J., Xu, K., Li, C., Ai, Q., Lu, W., Liang, H., Li, S. & He, J. (2020) Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol,* 21, 335-337.

Lillicrap, D. (2020) Disseminated intravascular coagulation in patients with 2019-nCoV pneumonia. *J Thromb Haemost,* 18, 786-787.

This article is protected by copyright. All rights reserved
Lousada, I., Comenzo, R.L., Landau, H., Guthrie, S. & Merlini, G. (2015) Light Chain Amyloidosis: Patient Experience Survey from the Amyloidosis Research Consortium. Adv Ther, 32, 920-928.

Lu, R., Zhao, X., Li, J., Niu, P., Yang, B., Wu, H., Wang, W., Song, H., Huang, B., Zhu, N., Bi, Y., Ma, X., Zhan, F., Wang, L., Hu, T., Zhou, H., Hu, Z., Zhou, W., Zhao, L., Chen, J., Meng, Y., Wang, J., Lin, Y., Yuan, J., Xie, Z., Ma, J., Liu, W.J., Wang, D., Xu, W., Holmes, E.C., Gao, G.F., Wu, G., Chen, W., Shi, W. & Tan, W. (2020) Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet, 395, 565-574.

Luo, P., Liu, Y., Qiu, L., Liu, X., Liu, D. & Li, J. (2020) Tocilizumab treatment in COVID-19: a single center experience. J Med Viral.

Madjid, M., Safavi-Naeini, P., Solomon, S.D. & Vardeny, O. (2020) Potential Effects of Coronavirus on the Cardiovascular System: A Review. JAMA Cardiol.

Manwani, R., Hegenbart, U., Mahmood, S., Sachchithanathan, S., Kyriakou, C., Yong, K., Popat, R., Rabin, N., Whelan, C., Dittrich, T., Kimmich, C., Hawkins, P., Schonland, S. & Wechalekar, A. (2018) Deferred autologous stem cell transplantation in systemic AL amyloidosis. Blood Cancer J, 8, 101.

Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q., Chang, J., Hong, C., Zhou, Y., Wang, D., Miao, X., Li, Y. & Hu, B. (2020) Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol.

Maurer, M.S., Elliott, P., Comenzo, R., Semigran, M. & Rapezzi, C. (2017) Addressing Common Questions Encountered in the Diagnosis and Management of Cardiac Amyloidosis. Circulation, 135, 1357-1377.

McLachlan, A.J., Cutler, D.J. & Tett, S.E. (1993) Plasma protein binding of the enantiomers of hydroxychloroquine and metabolites. Eur J Clin Pharmacol, 44, 481-484.

Mehra, M.R., Desai, S.S., Ruschitzka, F. & Patel, A.N. (2020) Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Lancet.

Mehta, P., McAuley, D.F., Brown, M., Sanchez, E., Tattersall, R.S., Manson, J.J. & Hlh Across Speciality Collaboration, U.K. (2020) COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet, 395, 1033-1034.

Merlini, G., Dispensieri, A., Sanchorawala, V., Schonland, S.O., Palladini, G., Hawkins, P.N. & Gertz, M.A. (2018) Systemic immunoglobulin light chain amyloidosis. Nat Rev Dis Primers, 4, 38.

Migrino, R.Q., Truran, S., Gutterman, D.D., Franco, D.A., Bright, M., Schlundt, B., Timmons, M., Motta, A., Phillips, S.A. & Hari, P. (2011) Human microvascular dysfunction and apoptotic injury induced by AL amyloidosis light chain proteins. American Journal of Physiology - Heart and Circulatory Physiology, 301, H2305-2312.
Mikael, J.R., Schuster, S.R., Jimenez-Zepeda, V.H., Bello, N., Spong, J., Reeder, C.B., Stewart, A.K., Bergsagel, P.L. & Fonseca, R. (2012) Cyclophosphamide-bortezomib-dexamethasone (CyBorD) produces rapid and complete hematologic response in patients with AL amyloidosis. Blood, 119, 4391-4394.

Moghadas, S.M., Shoukat, A., Fitzpatrick, M.C., Wells, C.R., Sah, P., Pandey, A., Sachs, J.D., Wang, Z., Meyers, L.A., Singer, B.H. & Galvani, A.P. (2020) Projecting hospital utilization during the COVID-19 outbreaks in the United States. Proceedings of the National Academy of Sciences of the United States of America.

Palladini, G., Hegenbart, U., Milani, P., Kimmich, C., Foli, A., Ho, A.D., Vidus Rosin, M., Albertini, R., Moratti, R., Merlina, G. & Schonland, S. (2014) A staging system for renal outcome and early markers of renal response to chemotherapy in AL amyloidosis. Blood, 124, 2325-2332.

Palladini, G., Kastritis, E., Maurer, M.S., Zonder, J.A., Minnema, M.C., Wechalekar, A.D., Jaccard, A., Lee, H.C., Bumma, N., Kaufman, J.L., Medvedeva, E., Kovacsovics, T.J., Rosenzweig, M.A., Sanchorawala, V., Qin, X., Vasey, S.Y., Weiss, B., Vermeulen, J., Merlini, G. & Comenzo, R.L. (2020) Daratumumab Plus CyBorD for Patients With Newly Diagnosed AL Amyloidosis: Safety Run-in Results of ANDROMEDA. Blood.

Palladini, G. & Merlina, G. (2019) When should treatment of AL amyloidosis start at relapse? Early, to prevent organ progression. Blood Adv, 3, 212-215.

Palumbo, A., Rajkumar, S.V., Dimopoulos, M.A., Richardson, P.G., San Miguel, J., Barlogie, B., Harousseau, J., Zonder, J.A., Cavo, M., Zangari, M., Attal, M., Belch, A., Knop, S., Joshua, D., Sezer, O., Ludwig, H., Vesole, D., Blade, J., Kyle, R., Westin, J., Weber, D., Bringen, S., Nieszvizky, R., Waage, A., von Lilienfeld-Toal, M., Lonial, S., Morgan, G.J., Orlowski, R.Z., Shimizu, K., Anderson, K.C., Boccardo, M., Durie, B.G., Sonneveld, P. & Hussein, M.A. (2008) Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia, 22, 414-423.

Pan, X.W., Xu, D., Zhang, H., Zhou, W., Wang, L.H. & Cui, X.G. (2020) Identification of a potential mechanism of acute kidney injury during the COVID-19 outbreak: a study based on single-cell transcriptome analysis. Intensive Care Med.

Perinel, S., Launay, M., Botelho-Nevers, E., Diconne, E., Louf-Durier, A., Lachand, R., Murgier, M., Page, D., Vermesch, R., Thierry, G. & Delavenne, X. (2020) Towards Optimization of Hydroxychloroquine Dosing in Intensive Care Unit COVID-19 Patients. Clin Infect Dis.

Pietrantonio, F. & Garassino, M.C. (2020) Caring for Patients With Cancer During the COVID-19 Outbreak in Italy. JAMA Oncol.
Pudusseri, A., Sanchorawala, V., Sloan, J.M., Bever, K.M., Doros, G., Kataria, S. & Sarosiek, S. (2019) Prevalence and prognostic value of D-dimer elevation in patients with AL amyloidosis. *American Journal of Hematology*, 94, 1098-1103.

Ritchie, A.I. & Singanayagam, A. (2020) Immunosuppression for hyperinflammation in COVID-19: a double-edged sword? *Lancet*.

Robilotti, E.V., Babady, N.E., Mead, P.A., Rolling, T., Perez-Johnston, R., Bernardes, M., Bogler, Y., Caldararo, M., Figueroa-Ortiz, C., Glickman, M., Joanow, A., Kaltsas, A., Lee, Y.J., Luca Bianchi, A., Mariano, A., Morjaria, S., Nawar, T., Papanicolaou, G.A., Predmore, J., Redelman-Sidi, G., Schmidt, E., Seo, S.K., Sepkowitz, K., Shah, M., Wolchok, J.D., Hohl, T.M., Taur, Y. & Kamboj, M. (2020) Determinants of Severity in Cancer Patients with COVID-19 Illness. *medRxiv*, 2020.2005.2004.20086322.

Roussel, M., Merlini, G., Chevret, S., Arnulf, B., Stoppa, A.M., Perrot, A., Palladini, G., Karlin, L., Royer, B., Huart, A., Macro, M., Morel, P., Frenzel, L., Touzeau, C., Boyle, E.M., Dorvaux, V., Le Bras, F., Lavergne, D., Bridoux, F. & Jaccard, A. (2020) A prospective phase II of daratumumab in previously treated systemic light chain amyloidosis (AL) patients. *Blood*.

Sanchorawala, V. (2019) Delay treatment of AL amyloidosis at relapse until symptomatic: devil is in the details. *Blood Adv*, 3, 216-218.

Sanchorawala, V., Sarosiek, S., Schulman, A., Mistark, M., Migre, M.E., Cruz, R., Sloan, J.M., Brauneis, D. & Shelton, A.C. (2020) Safety, Tolerability, and Response Rates of Daratumumab in Relapsed AL Amyloidosis: Results of a Phase II Study. *Blood*.

Sattianayagam, P.T., Lane, T., Fox, Z., Petrie, A., Gibbs, S.D., Pinney, J.H., Risom, S.S., Rowczenio, D.M., Wechalekar, A.D., Lachmann, H.J., Gilbertson, J.A., Hawkins, P.N. & Gillmore, J.D. (2013) A prospective study of nutritional status in immunoglobulin light chain amyloidosis. *Haematologica*, 98, 136-140.

Sharpley, F.A., De-Silva, D., Mahmood, S., Sachchithanantham, S., Ramsay, I., Garcia Mingo, A., Worthington, S., Hughes, D., Mehta, A., Kyriakou, C., Griffiths, P.D. & Wechalekar, A.D. (2020) Cytomegalovirus reactivation after bortezomib treatment for multiple myeloma and light chain amyloidosis. *Eur J Haematol*, 104, 230-235.

Shi, S., Qin, M., Shen, B., Cai, Y., Liu, T., Yang, F., Gong, W., Liu, X., Liang, J., Zhao, Q., Huang, H., Yang, B. & Huang, C. (2020) Association of Cardiac Injury With Mortality in Hospitalized Patients With COVID-19 in Wuhan, China. *JAMA Cardiol*.

Sidana, S., Tandon, N., Gertz, M.A., Dispensieri, A., Ramirez-Alvarado, M., Murray, D.L., Kourelis, T.V., Buadi, F.K., Kapoor, P., Gonsalves, W., Warsame, R., Lacy, M.Q., Kyle, R.A., Rajkumar, S.V., Kumar,
S.K. & Leung, N. (2019) Clinical features, laboratory characteristics and outcomes of patients with renal versus cardiac light chain amyloidosis. *British Journal of Haematology*, **185**, 701-707.

Stamatelopoulos, K., Georgiopoulou, G., Athanasouli, F., Nikolaou, P.E., Lykka, M., Roussou, M., Gaviropoulou, M., Laina, A., Trakada, G., Charakida, M., Delialis, D., Petropoulos, I., Pamboukas, C., Manios, E., Karakitsou, M., Papamichael, C., Gatsiou, A., Lambrinoudaki, I., Terpos, E., Stellos, K., Andreadou, I., Dimopoulos, M.A. & Kastritis, E. (2019) Reactive Vasodilation Predicts Mortality in Primary Systemic Light-Chain Amyloidosis. *Circulation Research*, **125**, 744-758.

Struck, R.F., Alberts, D.S., Horne, K., Phillips, J.G., Peng, Y.M. & Roe, D.J. (1987) Plasma pharmacokinetics of cyclophosphamide and its cytotoxic metabolites after intravenous versus oral administration in a randomized, crossover trial. *Cancer Res*, **47**, 2723-2726.

Tang, N., Li, D., Wang, X. & Sun, Z. (2020) Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*, **18**, 844-847.

Terpos, E., Ntanasis-Stathopoulos, I., Elalamy, I., Kastritis, E., Sergentanis, T.N., Politou, M., Psaltopoulou, T., Gerotziafas, G. & Dimopoulos, M.A. (2020) Hematological findings and complications of COVID-19. *Am J Hematol*.

Tett, S., McLachlan, A., Day, R. & Cutler, D. (1993) Insights from pharmacokinetic and pharmacodynamic studies of hydroxychloroquine. *Agents Actions Suppl*, **44**, 145-190.

Thorogood, N., Atwal, S., Mills, W., Jenner, M., Lewis, D.A., Cavenagh, J.D. & Agrawal, S.G. (2007) The risk of antimalarials in patients with renal failure. *Postgrad Med J*, **83**, e8.

Trachtenberg, B.H., Kamble, R.T., Rice, L., Araujo-Gutierrez, R., Bhimaraj, A., Guha, A., Park, M.H., Hussain, I., Bruckner, B.A., Suarez, E.E., Victor, D.W., Adrogue, H.E., Baker, K.R. & Estep, J.D. (2019) Delayed autologous stem cell transplantation following cardiac transplantation experience in patients with cardiac amyloidosis. *American Journal of Transplantation*, **19**, 2900-2909.

Vaduganathan, M., Vardeny, O., Michel, T., McMurray, J.J.V., Pfeffer, M.A. & Solomon, S.D. (2020) Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19. *N Engl J Med*.

Wang, W., Xu, Y., Gao, R., Lu, R., Han, K., Wu, G. & Tan, W. (2020a) Detection of SARS-CoV-2 in Different Types of Clinical Specimens. *JAMA*.

Wang, Y., Zhang, D., Du, G., Du, R., Zhao, J., Jin, Y., Fu, S., Gao, L., Cheng, Z., Lu, Q., Hu, Y., Luo, G., Wang, K., Lu, Y., Li, H., Wang, S., Ruan, S., Yang, C., Mei, C., Wang, Y., Ding, D., Wu, F., Tang, X., Ye, X., Ye, Y., Liu, B., Yang, J., Yin, W., Wang, A., Fan, G., Zhou, F., Liu, Z., Gu, X., Xu, J., Shang, L., Zhang, Y., Cao, L., Guo, T., Wan, Y., Qin, H., Jiang, Y., Jaki, T., Hayden, F.G., Horby, P.W., Cao, B. & Wang, C. (2020b) Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet*, **395**, 1569-1578.
Wechalekar, A.D., Gillmore, J.D. & Hawkins, P.N. (2016) Systemic amyloidosis. Lancet, 387, 2641-2654.

Wechalekar, A.D., Schonland, S.O., Kastritis, E., Gillmore, J.D., Dimopoulos, M.A., Lane, T., Foli, A., Foard, D., Milani, P., Rannigan, L., Hegenbart, U., Hawkins, P.N., Merlì, G. & Palladini, G. (2013) A European collaborative study of treatment outcomes in 346 patients with cardiac stage III AL amyloidosis. Blood, 121, 3420-3427.

Wechalekar, A.D. & Whelan, C. (2017) Encouraging impact of doxycycline on early mortality in cardiac light chain (AL) amyloidosis. Blood Cancer Journal, 7, e546.

Willan, J., King, A.J., Hayes, S., Collins, G.P. & Peniket, A. (2020) Care of haematology patients in a COVID-19 epidemic. Br J Haematol.

Yazdany, J. & Kim, A.H.J. (2020) Use of Hydroxychloroquine and Chloroquine During the COVID-19 Pandemic: What Every Clinician Should Know. Ann Intern Med.

Yu, J., Ouyang, W., Chua, M.L.K. & Xie, C. (2020) SARS-CoV-2 Transmission in Patients With Cancer at a Tertiary Care Hospital in Wuhan, China. JAMA Oncol.

Zagouri, F., Roussou, M., Kastritis, E., Koureas, A., Tsokou, E., Migkou, M., Gavriatopoulou, M., Nikitas, N., Gkotzamanidou, M., Terpos, E. & Dimopoulos, M.A. (2011) Lenalidomide-associated pneumonitis in patients with plasma cell dyscrasias. American Journal of Hematology, 86, 882-884.

Zappasodi, P., Dore, R., Castagnola, C., Astori, C., Varettoni, M., Mangiacavalli, S., Lazzarino, M. & Corso, A. (2007) Rapid response to high-dose steroids of severe bortezomib-related pulmonary complication in multiple myeloma. Journal of Clinical Oncology, 25, 3380-3381.

Zhang, C., Shi, L. & Wang, F.S. (2020a) Liver injury in COVID-19: management and challenges. Lancet Gastroenterol Hepatol, 5, 428-430.

Zhang, X., Song, K., Tong, F., Fei, M., Guo, H., Lu, Z., Wang, J. & Zheng, C. (2020c) First case of COVID-19 in a patient with multiple myeloma successfully treated with tocilizumab. Blood Adv, 4, 1307-1310.

Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., Xiang, J., Wang, Y., Song, B., Gu, X., Guan, L., Wei, Y., Li, H., Wu, X., Xu, J., Tu, S., Zhang, Y., Chen, H. & Cao, B. (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet, 395, 1054-1062.
Table 1: Multisystemic involvement in patients with AL amyloidosis and COVID-19 infection and how may impact management of patients with both conditions

| AL amyloidosis | COVID-19 | Special challenges in patients with AL amyloidosis |
|----------------|---------|-----------------------------------------------|
| **Heart**      | • Involved in most patients  
• Major determinant of prognosis  
• Cardiobiomarkers (NTproBNP/BNP & cardiac troponins) define risk of early death  
• Risk of sudden death is very high among stage 3B patients  
• Toxic free light chains can cause direct myocardial cell apoptosis, reflected by elevated cardiac troponin levels  
• Low arterial blood pressure is common and associated with worse prognosis  
• Most patients (especially with more severe cardiac amyloidosis) have very poor tolerance of standard drugs for heart failure  
• Paradoxical vasodilation may occur and is associated with risk of early death | • Cardiovascular complications are common in severe disease.  
• Myocardial injury (Zhou, et al 2020), including fulminant myocarditis with cardiogenic shock,  
• Associated atrial and ventricular arrhythmias (Driggin, et al 2020, Hu, et al 2020). | • Patients with SARS-CoV2 infection and preexisting cardiovascular disease are at increased risk of severe complications and death (Driggin, et al 2020, Guo, et al 2020, Shi, et al 2020).  
• Poor tolerability of standard therapies for heart failure, such as β-blockers and ACE inhibitors in patients with AL amyloidosis.  
• Therapies such as hydroxychloroquine / chloroquine with or without azithromycin (Driggin, et al 2020) have been associated with QT prolongation, risk of drug-induced torsades de pointes and drug induced-sudden cardiac death.  
• Risk of drug-induced arrhythmias can be amplified if multiple medications, which prolong QTc are
| Kidneys | Acute kidney injury is common among patients with severe COVID-19 (Guan, et al 2020) (Chen, et al 2020c) | Depleted intravascular volume and reduced vascular tone during cytokine storm may increase the risk of acute renal failure; |
| --- | --- | --- |
| Kidneys | Nephrotic range proteinuria, associated with low blood pressure, peripheral edema and effusions | Proteinuria may develop in up to 43.9% of infected patients, especially those with AKI(Cheng, et al 2020) |
| Kidneys | Urine loss of immunoglobulins | SARS-CoV-2 can be detected in the urine of patients with severe COVID-19 (Guan, et al 2020). |
| Kidneys | Increased thrombotic risk | co-expression of ACE2 and TMPRSS genes in podocytes and proximal straight tubule cells, indicates that kidney is a target of SARS-CoV-2. |
| Kidneys | | Dosing of several drugs may need be adjusted to degree of renal dysfunction. |
| Kidneys | | up to 50% of chloroquine and 15% to 25% of total clearance of hydroxychloroquine is done by the kidneys(Tett, et al 1993) |
| Kidneys | | These drugs are not dialyzable(Jallouli, et |
| Peripher al blood | • Cytopenias are uncommon and associated with use of chemotherapy  
• the coagulation and fibrinolytic system are often deregulated due to sequestration of clotting factors and loss of fibrinolytic and anticoagulation factors in urine  
• small vessels may be dysfunctional due to amyloid deposition  
• Atrial arrhythmias predispose to cerebrovascular complications | • lymphopenia is common and associated with prognosis  
• coagulation disorders are relatively common mostly among patients with severe disease: elevated D-dimers and their gradual increase are associated with poor prognosis.  
• Disseminated intravascular coagulation (DIC) has been described other thrombotic complications have  
  | • Thromboprophylaxis is highly recommended for hospitalized patients with COVID-19  
• Thromboprophylaxis improve outcome  
• thromboprophylaxis with LMWH or fondaparinux is suggested over unfractionated heparin to reduce contact unless the patient is judged to be at increased bleeding risk  
• in AL patient with COVID-19 the use of thromboprophylaxis is bound to plasma proteins (McLachlan, et al 1993)  
• For dialysis-dependent patients, measures to reduce COVID-19 risk in dialysis facilities should be followed (Kliger and Silberzweig 2020).  
• Patients with kidney transplants may be at higher risk of severe COVID-19 |
| Liver |
|-------|
| • Hepatic involvement is common, but the clinical manifestations are usually mild; |
| • Amyloid is deposited in the parenchyma, along the sinusoids within the space of Disse, or in blood vessel walls; compressing hepatocytes. |
| • Symptomatic involvement, including rupture, portal hypertension or hepatic failure, is rare. Most common manifestations include hepatomegaly and increased cholestatic enzymes. |
| • Limited data from China indicate increased risk of acute liver injury among patients with viral hepatitis during COVID-19 (Guan, et al 2020). |
| • Cirrhotic patients may have higher risk of COVID-19 infection |

| GI |
|-----|
| • Diarrhea, constipation or alternating are commonly found |
| • May be due to direct intestinal involvement or due to autonomic system involvement |
| • Malabsorption, poor nutritional status and SARS-CoV-2 binds to ACE2 and TMPRSS2 that are expressed in small intestine |
| • ACE2 is expressed in the upper esophagus and colon. |
| • Viral RNA may be shedding in stool. |
| • In patients with chronic diarrhea, symptoms from GI associated with COVID-19 may evade |
| • Patients at poor nutritional status and sarcopenia may be at higher risk to acquire |
| Sarcopenia | Diarrhea in common incidence rate of diarrhea is 2% to 50%. Diarrhea may precede or present along with the respiratory symptoms. | infection and have worse prognosis when infected by SARS-CoV-2 |
|------------|------------------------------------------------------------------------------------------------|-------------------------------------------------|

**Peripheral Nerve**

- Peripheral and autonomic neuropathy are common in patients with AL amyloidosis.
  - different types of peripheral neuropathy may occur depending on major symptoms and clinical findings.
  - symptoms of neuropathy may deteriorate during therapy with bortezomib or thalidomide.
- limited data
  - in a retrospective series, 36.4% of the patients had neurologic manifestations, mostly among patients with severe infection,
  - acute cerebrovascular diseases, impaired consciousness and rhabdomyolysis were the most common
  - 8.9% had PNS symptoms, most common being taste and smell impairment.
- The risk cerebrovascular complications seem to be increased in patients with COVID-19
- and this risk of cerebrovascular complications is increased in COVID-19 and AL amyloidosis, especially those with cardiac involvement who are at risk of atrial arrhythmias.

This article is protected by copyright. All rights reserved
Table 2: summary of suggestion for the treatment of AL amyloidosis during the pandemic

| Suggestion                                                                                       |
|--------------------------------------------------------------------------------------------------|
| The risk of acquiring the infection is not the same across different regions                     |
| AL amyloidosis is a deadly disease; delays in the diagnosis and initiation of therapy should be avoided if possible. |
| Therapy for AL amyloidosis should start upon confirmation of the diagnosis with few exceptions.  |
| Indications to start therapy should not change, especially in patients with heart involvement     |
| For low risk patients, a short delay, until local control of the outbreak, may be reasonable      |
| In relapsing patients, with slow increase and relatively low levels of FLCs, without heart involvement, could probably wait and avoid frequent hospital visits. |
| Omitting bortezomib for MDex is not recommended, since a randomized study showed that BMDex is associated with faster and deeper responses and longer survival than MDex |
| Using SC bortezomib instead of IV reduces toxicity and in-hospital time and may be delivered in outpatient setting |
| Oral instead of IV cyclophosphamide has similar pharmacokinetics and efficacy                     |
| Prophylactic growth factors might be considered in selected patients receiving potentially myelotoxic therapy. |
| Daratumumab should be given at lower volumes (500 ml) and in shorter time (90 min) after the first few infusions, provided that no major infusion-related reactions occurred. |
| Daratumumab discontinuation may be considered in patients in complete response or after 2 years of therapy. |
| Cannot substitute bortezomib with ixazomib, at least in previously untreated patients or those with severe cardiac involvement. |
| In patients with relapsed disease, ixazomib-based therapy is reasonable                           |
There is no data to support any dose modifications of any of the oral anti-plasma cell drugs (IMiDs, ixazomib, alkylating agents)

In selected patients, who have achieved a satisfactory hematologic response and/or organ response, earlier completion of therapy or a less intensive schedule may be reasonable.

Steroid dose can be reduced or discontinued in patients on long term lenalidomide.

If HDM/ASCT is planned, delaying or deferring the transplant may be a safer approach.

Hospital visits for follow up evaluation should be reduced to those necessary, depending on local conditions and standards. Using local laboratories may be feasible in some areas.

Specialized testing can be usually postponed for stable patients in hematologic remission and reserved for those in which a major treatment decision needs to be made.

Home measurement of weight, pulse rate and blood pressure should be encouraged and can be helpful to manage heart failure in many patients.

Telemedicine may be helpful, but has major limitations in a rare and complex disease such as AL amyloidosis.