

# Recommendations for patients with chronic neutropenia and constitutional marrow failure disorders

such as Fanconi Anemia, Diamond Blackfan Anemia, Schwachman-Diamond Syndrome, Telomere biology disease, Telomere biology disease and Gaucher disease

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## Suggestions for patients with Neutropenia and Constitutional Marrow Failure Disorders during COVID-19 pandemic

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General measures as those indicated in “Introduction SARS-CoV-2 and Specific aspects for hematologists and oncologists” of the [FAQ by the EHA Scientific Working Group on Infections in Hematology](#), are considered as valid.

Another general measure is to access Hospitals only for urgent, undeferrable needs not manageable by other routes. This is because the risk of contagion of COVID-19 is higher in hospitals and because it should be avoided to distract medical staff from real emergencies. One of the undeferrable need, to be balanced with the advantages of staying away from hospitals, is the risk of bacterial sepsis. In this respect it is suggested to contact the specialist center physician for a more accurate balance of risk/benefit ratio.

Whenever possible homecare service for manageable treatments (e.g. transfusions, antibiotic /antifungal infusions) and monitoring tests should be preferentially used.

We know that the general pediatric population is far less susceptible to COVID -19 (0.9-1.2%) compared to adults [1] and that the disease usually occurs in a milder form than in adults, although children are reported to be a potential asymptomatic reservoir of the disease.

### 1. Chronic neutropenias

#### 1.1. Children

No specific data are available regarding COVID-19 in children with neutropenia. However, even if in general patients with chronic isolated neutropenia have no increased risk of viral infections, some patients with congenital forms have in the past been reported to suffer from severe viral infections.

This includes subjects with WHIM syndrome or with genetic backgrounds (like GATA-2, Schwachman Diamond syndrome-SDS-) associated with some degree of immune deficiency who presented with chronic bronchitis.

For these reasons, these categories might be considered to have a high risk of severe COVID-19. Although, i.v Immunoglobulins do not confer specific protection against COVID-19, they may be beneficial as a general

supportive measure to the immunological status in patients in whom neutropenia is associated with some degree of immune-deficiency.

In case of COVID-19 it is important to have sufficient granulocytes to fight secondary bacterial infections. Therefore, we suggest paying close attention to neutrophil counts, to maintain values permanently above 1000/ $\mu$ l and, if necessary, to adjust the G-CSF dose. Excess dosage should be avoided because of the risk of over-inflammatory response in affected organs (e.g. the lung) leading to exaggerated tissue injury.

Patients with autoimmune neutropenia are not reported to be at higher risk of severe viral infections. For those who are on immunosuppressive treatment (e.g. MMF, Sirolimus) any change of immune suppression should be discussed with doctors of the specialist Center who has the patient in charge. Neutrophil count should be steadily maintained above 1000/ $\mu$ l. A slightly higher ANC might be advisable in case of bacterial infection not subsiding to antibiotics, but G-CSF over-dosage must be avoided. A dose of 3 mcg/kg is generally considered effective and safe in these cases.

## **1.2. Adults**

Reports from literature indicate that adult neutropenic patients have high rates of influenza complications [2].

Observations from cohorts of these subjects does not currently show increased vulnerability to COVID-19 infection too. The standard precautions should be taken by these patients. In case of COVID-19 infection, G-CSF should be given to keep absolute neutrophil counts above 1000/ $\mu$ l. Individual dose adjustment may be needed but excess dosage should be avoided because of the risk of over-inflammatory response in affected organs (e.g. the lungs) leading to exaggerated tissue injury.

## **2. Constitutional Marrow Failure Disorders** (like Fanconi Anemia, Diamond Blackfan Anemia, Schwachman-Diamond Syndrome, Telomere biology disease).

For Constitutional Marrow Failure patients who are in need of an urgent, undeferrable Stem Cell Transplantation (SCT) we recommend to refer to [EBMT indications](#), bearing in mind that for those who are in aplastic phase, transplant has to be considered an urgent, non-deferrable indication similar to what occurs in patients with acquired aplastic anemia.

For those patients who are not in need of an urgent, undeferrable SCT, it should be advisable to avoid initiating treatments likely to reduce lymphocytes, like high dose steroids.

For Diamond Blackfan anemia a comprehensive guidance has been elaborated by the Hemoglobinopathy and DBA panel of the British Society of Haematology (NHP COVID-19 Guidance for patients with Diamond Blackfan anemia, NHP COVID-19 Guidance: Patients Version).

Patients with Schwachman Diamond and GATA2 syndrome and those with an associated immune deficiency/dysregulation have in the past been reported to suffer from severe viral infections and may thus be considered at increased risks of severe COVID-19. Lymphopenia, often present in Constitutional Marrow Failure Disorders, is another risk factor of severe COVID-19.

Although i.v Immunoglobulins do not confer specific protection vs COVID-19, they may be beneficial as a general supportive measure to the immunological status.

As a general rule, we recommend for Constitutional Marrow Failure patients to discuss with their specialist Center physician the risk/benefit balance inherent in any treatment change.

For Gaucher disease, see Addendum 1.

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## Addendum 1: Gaucher Disease and SARS-CoV2 infection

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### What is the risk for a patient with Gaucher Disease to become infected with SARS-CoV2 and what is the risk to have a severe disease course?

The [FAQ by the EHA Scientific Working Group on Infections in Hematology](#) works for Gaucher Disease (GD) concerning the following points:

- Current available data does not show a different rate of infection in patients with GD, compared to healthy members of the general population [1,2]. This is mostly due to the fact that, GD patients, as well as healthy individuals are immunologically naïve to this novel pathogen and there are no data on re-infection or disease reactivation of a previously cured patient.
- Regarding the course of the infection, underlying GD has not been identified as an independent risk factor in multivariate analyses so far [2].

#### However

GD is a multisystem disease and patients suffering from it are anticipated to be at risk of a more severe course of COVID-19 disease and complications, related to numerous factors.

1. GD patients show multiple types of immune abnormalities associated to T- and B-lymphocytes with respect to their subpopulations and their cytokine profile [3], as well as memory, regulatory and activation markers [4] and additionally, they have dendritic cell dysregulation [5]. They also exhibit a chronic pro-inflammatory status, which has been blamed for the increased incidence of autoimmune and lymphoproliferative disorders - particularly multiple myeloma – observed among them. The chronic inflammatory state is characterized by various findings of lymphocyte and monocyte activation, increased serum cytokine levels, especially IL-6, IL-1 $\beta$ , TNF- $\alpha$ , and IFN- $\gamma$  [6] as well as by elevated serum acute phase protein levels and altered platelets and coagulation pathways [7]. These findings are more prominent among treatment-naïve or among patients who have recently started specific treatment. Whether these findings have clear clinical consequences and put GD patients at higher risk for the manifestation of a hyperimmune response, with a Hemophagocytic Lymphohistiocytosis (HLH)-like cytokine storm phase and disseminated intravascular coagulopathy, following COVID-19 infection remains unknown as yet [2]. The above-mentioned points / speculations should be considered, and they clearly need further clinical studies and careful observation to be verified or clarified. Interestingly, these immune alterations and biomarker levels do not correlate with GD clinical type or disease bulk, but rather represent a constitutive feature of the disease [4,6]. However, according to some reports, they tend to be more severe in treatment-naïve patients, and ERT may reverse some of these immune abnormalities, depending on the dose and duration of therapy [8,9]. Since patients with underlying comorbidities, particularly those with a condition affecting immune response, are reported to have a higher risk of developing severe complications in CARV infections [10], GD patients, especially if treatment-naïve or undertreated, might be at higher risk of a more severe course of COVID19 infection, with potential higher severity of respiratory failure and/or other vital organ dysfunction, than the general population.

2. Splenectomy in GD patients is associated with further impairment of their immune function, and it is anticipated that splenectomized patients might be at higher risk of severe COVID-19 disease [8].
3. Lower respiratory pneumonia and ARDS are reported as the major morbidity and the most severe complications of COVID-19 infection, and respiratory failure is the leading cause of mortality [10,11]. This fact puts GD patients with interstitial pulmonary disease, those with neuronopathic types of the disease, with or without convulsions, and finally patients with severe chest wall and spine deformities at increased risk for development of severe and progressive pulmonary complications of COVID-19 disease.
4. Cardiovascular disease is reported to occur as a complication of COVID-19 disease, occurring in 20% of critically ill patients [11]; and COVID-19 disease has been reported to be more severe in patients with pre-existing cardiovascular illness [12]. In a small proportion of affected patients, the virus infects other tissues and vital organs, and induces severe infections, such as myocarditis and encephalitis but this cannot be predicted. Therefore, considering these published data, GD patients with pulmonary hypertension, type 3 GD patients with cardiomyopathy and D409H genotype with valvular and myocardial calcification should be considered at higher risk of cardiac decompensation if they develop COVID-19 infection.
5. Hepatic enlargement is common in Gaucher disease (however, hepatic fibrosis/cirrhosis, portal hypertension/veno-occlusive disease and steatohepatitis are uncommon complications of GD [13]) which could put patients at higher risk of more hepatic damage, as COVID-19 is reported to be associated with variable degrees of hepatic injury [11,14]. However, how underlying liver conditions could influence further liver injury in COVID-19 infected patients needs to be meticulously evaluated [14].
6. In the COVID-19 pandemic, age is an important prognostic factor [1,2,11] which, most probably, will not apply to type 3 GD patients, with childhood onset multisystem involvement. However, elderly patients with GD should be particularly cautious as this is also applies to the general elderly population.
7. The potential effect of Enzyme Replacement Therapy (ERT) or Substrate Reduction Therapy (SRT) as prognostic factors, driving the disease pattern and prognosis of COVID-19 in GD patients, needs to be carefully studied.

### **What can be done to prevent COVID-19 infection or to attenuate its severity? Who should have therapy for GD deferred or interrupted?**

- ERT for GD treatment in types 1 and 3 is mandatory and beneficial; does not impair host antiviral defense; has not been associated with increased incidence of any type of infection; and should be given as indicated and scheduled. ERT given in the standard dose is known to improve the immunological profile, as well as the hematological profile of the patients; and generally improve organ functions to varying degrees, according to type and severity of the disease and the age at onset of therapy [6,7,13]. Therefore, GD therapy on ERT should be maintained on full dose – as scheduled prior to infection – hand in hand with COVID-19 related therapy, as evidenced in previous case reports showing beneficial value of ERT, in addition to specific anti-infection management [19,20].
- GD patients on SRT-Eliglustat, once diagnosed as COVID-19 positive, should refer to their treating physician for evaluation of the decision to continue or interrupt therapy; Eliglustat is not recommended for patients with pre-existing cardiac disease, with long QT syndrome or for patients on anti-arrhythmic drugs [15]; COVID-19 associated cardiac injury and arrhythmias have been reported in critically ill patients with increased mortality risk [16]. Therefore, for GD patients on SRT-Eliglustat, the decision to give the drug or withhold should be taken by the GD treating physician, considering drug-drug interactions and the importance of drug monitoring [21,22,23].

- For patients on SRT-Miglustat no cardiac, but mainly gastrointestinal and minor neurological adverse events, have been reported. Therefore, such patients could continue receiving miglustat and keep continuous communication with their treating physicians.
- Intravenous Immunoglobulin (IVIg) has no preventive role in patients with GD, as hyper- rather than hypogammaglobulinemia is frequently reported among them [17]. Physicians need to be aware that IVIg products are NOT specifically effective against SARS-CoV2 – because of a lack of specific antibodies within the products – but when indicated, they help to generally restore a defective immune response and help to prevent additional (for example bacterial) infections. However, as time elapses, there is a high probability that new preparations from immune donors will include protective antibodies against SARS-CoV2 as well.
- Prophylactic antibiotics have no rationale and are not generally recommended. In contrast, vaccination against influenza, as well as against pneumococci, should be recommended for all GD patients and particularly for those who have been splenectomized, as per current guidelines.
- Nutritional support is of great importance, especially in treatment-naïve or recently treated patients, with evidence of hypermetabolic state and/or malnutrition and in type 3 disease with pseudobulbar palsy and nutritional difficulties [18].

### **How long should precautions last?**

- In individual GD patients with active COVID-19 infection, precautions, regarding antineoplastic therapy, should last if possible until there are no more clinical signs of ongoing infection and the patient has been tested negative for SARS-CoV2 twice. However, the need and urgency of administration of any antineoplastic kind of treatment, should be cautiously judged and balanced against the potential irreversible harm, resulting from its delay. The final decision should be taken on an individual basis. General precautions in the population depend on guidance by WHO and national health authorities. Some experts assume that the critical time of the pandemic will last 2-4 months, if measures of clear-cut social distancing are effectively maintained.

### **What diagnostic measures should be taken for somebody who shows symptoms of RTID/LRTID?**

The EHA statement for COVID19 and malignancy is the same for Gaucher disease concerning the following points:

- In someone presenting with symptoms of RTID, broad diagnostics (ideally SARS-CoV-2 in addition to multiplex-NAT, including other CARV like influenza, parainfluenza, metapneumo- and human coronaviruses and respiratory pathogens like pneumococci) are strongly recommended [10,24]. Identification of the infectious agent, even if it is not SARS-CoV-2, is imperative; has therapeutic and regulatory consequences; and should thus be obtained.
- We are aware that national recommendations regarding testing for SARS-CoV-2 may differ and that shortages of tests may become a problem. However, we recommend that GD patients with cancer should be generously tested, since the detection of COVID infection has immediate implications to their treatment strategy.
- Samples should generally be taken from the involved anatomical area. Nasopharyngeal aspirates, samples from the lower respiratory tract and nasopharyngeal swabs may be used, whereas nasal swabs alone confer a lower sensitivity [25]. Clinicians should be aware, that testing for SARS-CoV-2 might

produce false negative results in asymptomatic or mildly symptomatic patients and in patients with LRTID, if samples from the upper respiratory tract are tested [26,27]. Therefore, it is very important to implement standardized sampling and to repeat tests in patients with unexpected results, to avoid bias by pre-analytical mistakes.

- For diagnosis of LRTID in patients with CARV infection including SARS-CoV-2, CT scans should be used rather than chest X ray [27,28]. If LRTID is present, patients should undergo standard microbiological testing to test for bacterial or fungal superinfection, since superinfection is the most dangerous complication in any CARV-infection [1,2,11].

**However,**

specific points need to be considered in GD:

- For GD patients, assessed for COVID-19 diagnosis, there is overlapping inflammatory response in both conditions, regarding some biochemical parameters, such as hypercytokinemia, and increased serum CRP, D-dimers and ferritin levels, which therefore, may not be used as diagnostic or prognostic indices of COVID-19 infection in GD patients [8,9,11,12,25,26].
- Radiological findings of interstitial pulmonary infiltrate occur early in COVID-19 pneumonia, but to some degree can be present in GD patients with pulmonary involvement, in the absence of COVID-19 infection. However, this is not true for the typical radiological findings of ARDS in COVID-19 infection, which cannot rather easily become misinterpreted as interstitial lung involvement, attributed to the pre-existing GD [27,28].
- A GD patient with proven COVID-19 infection, should be initially evaluated for pre-existing hepatic, renal, cardiac, neurological and pulmonary disease, which should be closely monitored during the course of infectious illness. In COVID-19 infection, mortality has been reported to be higher among patients with pre-existing chronic organ diseases [13,18].

### **What general therapeutic measures need to be taken in somebody who has GD and is infected with SARS-CoV2?**

Same as in malignancy:

- Supportive care: hydration, proper nutrition, paracetamol antipyretics, inhaled bronchodilators, oxygen when needed.
- All patients with severe COVID-19 should be screened for hyperinflammation using laboratory tests (e.g. increasing ferritin, decreasing platelet counts, or erythrocyte sedimentation rate) to identify the subgroup of patients for whom immunosuppression could improve mortality. Therapeutic options include steroids, intravenous immunoglobulin, selective cytokine blockade (e.g. anakinra or tocilizumab) and JAK inhibition [29].

### **How can COVID-19 infection be treated specifically?**

Same as in malignancy:

- There are no established standard treatments for COVID-19 infection, since this is a new disease. Whenever possible, patients should be included into clinical trials. Infectious disease specialists should always be involved in the therapeutic decisions. If experimental treatment with drugs approved for

other indications, such as chloroquine, colchicine or tocilizumab is considered, physicians should share the decision with their patients and inform them about the chances and risks of such strategies.

- Experiences with SARS and first experiences with SARS-CoV-2 suggest efficacy of some treatment options: lopinavir/ritonavir, chloroquine and remdesivir seem most promising [30]. Ribavirin is potentially effective based on *in silico* models, but no clinical data is available. For SARS, retrospective data with low quality of evidence suggested effectiveness of ribavirin in combination with lopinavir/ritonavir.
- If specific treatment is administered it should probably be given as early as possible to be effective, similar to treatment of influenza.
- Blood products, although now rarely indicated as treatment in patients with GD, need to be administered with caution because there is emerging evidence that COVID-19 might be transmitted through the plasma [31,32]. If this is verified, examination of donated products for the presence of this virus might become mandatory, although at present, such guidance is not applied [33].
- Convalescent plasma has been tried as a potential therapy for COVID-19 and is recently FDA approved [34].
- Extracorporeal membrane oxygenation has been suggested for COVID19 patients with ARDS [35].

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