

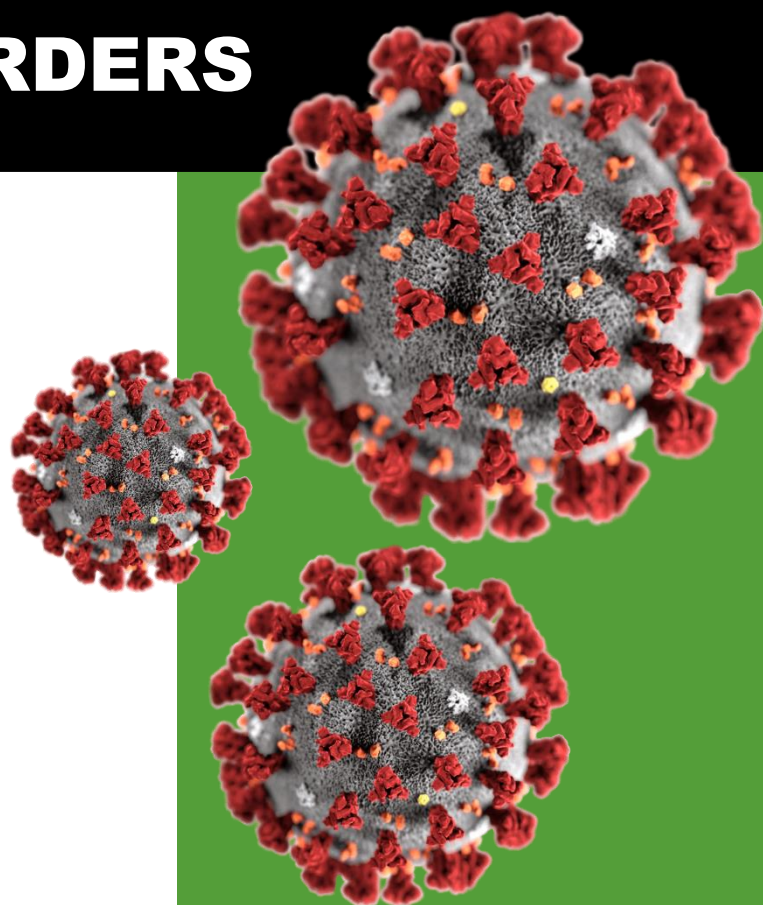
THE COVID-19 PANDEMIC AND HAEMOGLOBIN DISORDERS

Thalassaemia & Sickle Cell Disease: Classification of Risk Groups & Other Considerations

Guidance for Patients,
Parents & Healthcare
Professionals



THALASSAEMIA
INTERNATIONAL
FEDERATION



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CONTENTS

EXECUTIVE SUMMARY	3
INTRODUCTION	4
THE POSITION OF THALASSAEMIA INTERNATIONAL FEDERATION (TIF)	6
GUIDANCE FOR PATIENTS WITH THALASSAEMIA SYNDROMS	8
RISK LEVELS	8
GROUP A – PATients at ‘moderate risk’	8
group b – patients at ‘high risk’	8
GROUP C – PATIENTS AT ‘HIGHEST RISK’	9
ASSOCIATION OF RISK LEVEL WITH SAFETY AT WORK / SCHOOL / EDUCATION	10
GROUP A - Patients at “moderate risk”	10
GROUP B - Patients at “high risk”	11
GROUP C - Patients at “highest risk”	11
ADVICE TO THE ACCIDENT & EMERGENCY DEPARTMENTS (A&E)	12
GENERAL ADVICE FOR PATIENTS WITH THALASSAEMIA	12
HAEMOGLOBIN H DISEASE IN THE COVID-19 PANDEMIC	14
ADVICE ON BLOOD TRANSFUSION	15
INFORMATION FOR TRANSPLANTED PATIENTS	16
TREATMENT OF COVID-19 IN PATIENTS WITH B-THALASSAEMIA	17
SPLENECTOMISED PATIENTS	17
GUIDANCE FOR PATIENTS WITH SICKLE CELL DISEASE (SCD)	21
CLINICAL KEY ELEMENTS OF SCD INCLUDE:	22
COVID-19 & SCD	22
MANAGEMENT OF SCD WITH OR WITHOUT COVID-19 DURING THE PANDEMIC	23
MANAGEMENT OF PATIENTS WITH SCD & POSSIBLE COVID-19 INFECTIONS	23
patients with scd admitted to hospital with covid-19 proven or suspect infection (fever, respiratory symptoms)	24
patients with scd presenting to hospital with covid-19 related symptoms	25
some practical advice for outpatient care OF ASYMPTOMATIC PATIENTS	26
ASPLENIA / HYPOSPLENIA	28
RISK OF SEVERE COURSE OF COVID-19	28
ASSISTANCE IN THE FACE OF THE THREAT FROM COVID-19	29
CHANGE OF SUPERVISION WHEN PROOF OF SARS-CoV-2	29
SPLENECTOMISED PATIENTS	29
ADVICE ON BLOOD TRANSFUSION	32
TIF COVID-19 Help Desk & Communication Line	33

EXECUTIVE SUMMARY

This document, compiled by the Thalassaemia International Federation (TIF) with the guidance and support of its International Scientific Advisory Board and other collaborators seeks to:

- a) Provide a classification of risk levels that may be applied to thalassaemia and sickle cell disease patients and which depends largely on age, co-morbidities and overall general health;
- b) Bring together published information on risk factors and best practices for the management of patients in the time of the pandemic (either for disease-related issues or COVID-19 infection) and;
- c) Alert and inform all stakeholders of the plethora of aspects that affect the lives of patients with thalassaemia and sickle cell disease consequent to the pandemic and related to their conditions, medical and social needs (e.g. transfusion practices, routine monitoring tests, outpatient care, emergency care, social support and care etc);

It is noted that the information presented constitutes an amalgamation of practices and recommendations that have been either published in peer-reviewed journals, and/or national government or professional society websites and/or national patient NGOs and include mainly the UK, Germany, France, USA, Italy and Cyprus.

Moreover, we hope that the TIF suggested risk classification of patients (see page 8) will serve only as a basic guide for patients, healthcare professionals and policy-makers in their decisions during the COVID-19 pandemic throughout lockdown, in the period involving the relaxation of restrictive measures and beyond.

However, we must highlight that regardless of risk group, all patients with haemoglobin disorders should be considered amongst the 'vulnerable' groups of society, and measures should be taken to facilitate their accessibility to healthcare necessary to their needs in a safe and an uninterrupted way.

INTRODUCTION

Individuals with haemoglobin disorders are classified as ‘vulnerable’ groups of patients in the greatest majority of countries worldwide. The inclusion of different chronic diseases in the national list of ‘vulnerable’ population is based on recommendations by the World Health Organisation (WHO)¹ and other official health bodies with relevant international expertise and knowledge. Final adoption nevertheless, lies in the decisions taken by the Governments through their competent national health authorities and their national scientific/academic/medical/social/economic advisors.

However, Thalassaemia International Federation (TIF)² has a clear position on the matter based on the opinion and recommendations of its International Medical Advisory Panel: All patients with haemoglobin disorders, wherever they may live, should be included amongst the ‘vulnerable’ groups of every country’s population³. In this context, special recommendations for their safety and protection in the course of the COVID-19 pandemic, both with regards to medical as well as to social care, are necessary to be drafted by the competent authorities in every country and well disseminated to patients, families and health care professionals in the care of haemoglobin disorders.

Such guidance and recommendations require the involvement and contribution of treating medical specialists, patients themselves and decision makers at the level of the Ministry of Health, Ministry of Labour, Ministry of Finance and Ministry of Education. In addition, for the delivery of many non-medical, ‘at home’ services to the ‘vulnerable’ groups of the society, many philanthropic and voluntarism based NGOs have been widely engaged.

1

https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf?sfvrsn=1ba62e57_10

² The Thalassaemia International Federation (TIF) is a patient-oriented non-profit, non-governmental umbrella federation, established in 1986 with Headquarters in Nicosia, Cyprus. TIF’s mission is to help ensure equal access to quality health and other care for every patient with thalassaemia and other haemoglobin disorders around the world. To-date membership boasts 232 members from 64 countries across the globe. TIF works in official relations with the World Health Organization (WHO) since 1996 and enjoys active consultative status with the United Nations Economic and Social Council (ECOSOC) since 2017. Moreover, it is a strategic partner of the European Commission under the Third Health Programme since 2018 and a member of the Patients and Consumers Working Party (PCWP) of the European Medicines Agency (EMA) since 2010. In 2019, TIF obtained a participatory status at the Council of Europe, as a Member of the Conference of International NGOs. Moreover, TIF was awarded, in the context of the 68th World Health Assembly in May 2015, the ‘Dr Lee Jong-wook Memorial Prize’ for its outstanding contribution to public health.

³ TIF POSITION STATEMENT “COVID-19: Inclusion of thalassaemia and Sickle Cell Disease patients in the high risk population” https://thalassaemia.org.cy/wp-content/uploads/2020/04/TIF-Position-Statement_Thal-SCD-High-Risk-Group-1.pdf

The information in this document is only a compilation of recommendations or better guiding information with regards to COVID-19 and Haemoglobin Disorders retrieved from published information found in either peer reviewed papers or at official government sites of some Western countries mainly including the UK, Germany, Italy, France, Cyprus and the USA. Unfortunately, published data and information with regards to COVID-19 and haemoglobin disorders is very confined in general but even more in countries of the developing world where sadly lives more than 75% of the global community of patients with haemoglobin disorders. As a consequence, some or even many of these recommendations or part of the guiding information may not be possible to be fully adopted by many or even the majority of the countries of the developing world. However, TIF in the context of its ongoing support to its global members since the beginning of the COVID-19 pandemic, felt the responsibility to disseminate such information which it considers as a valuable and reliable tool on which to build upon while it acknowledges the need to monitor and update this, on a continuous basis as new information emerges from across the globe.

CARRIERS of any haemoglobin disorders are NOT CONSIDERED as 'VULNERABLE' or individuals 'AT RISK'⁴. They are healthy individuals and will only be considered 'vulnerable' or 'at risk' if they have an underlying condition, such as any other member of the community may have either due to age and/ or any acquired chronic disease/condition⁵.

⁴ <https://ukts.org/covid19faq/>

⁵ <https://www.sicklecellsociety.org/coronavirus-and-scd/#Shielding>

THE POSITION OF THALASSAEMIA INTERNATIONAL FEDERATION (TIF)

Patients with thalassaemia and sickle cell disease (SCD) are likely to be at increased risk of complications from COVID-19. There is a broad spectrum of severity of these syndromes due to the various mutations and combinations of mutations which cause them. In addition, each patient has a different expression of the disorder on account of the vast heterogeneity of the quality of medical care provided worldwide (in particular in the developing countries) but also on account of challenges related to adherence to treatment, socio-economic status and migration conditions / aspects and which are met both in the Western world and across the globe.

An effort has been made to classify the level of risk around these patients albeit this is only a basis to support health care professionals, decision making authorities and health care systems in every country particularly beyond the Western world to build on and develop their own national recommendations or guiding documents. In addition, every single patient with a haemoglobin disorder, on account of the disorders' nature, genetic background, complicated pathophysiology and consequently its vastly heterogeneous clinical outcome, requiring almost personalized or tailored to individual needs recommendations and care, certainly constitutes a different case on its own, and the key responsibility of each patients' management lies with the long-term treating specialist.

Considering the above, patients with haemoglobin disorders can be broadly and even grossly divided into three Groups (albeit this classification is more applicable to thalassaemia than sickle cell disease patients, who are all considered in the 'highest risk' group:

- ❖ **GROUP A - Patients at “moderate risk”**

- ❖ **GROUP B - Patients at “high risk” and**

- ❖ **GROUP C - Patients at “highest risk”**

The recommendations/guiding information that follow are relevant to:

- i. β -thalassaemia (β homozygous [i.e. thalassaemia major], β intermedia);
- ii. Combined forms of thalassaemia such as β -thalassaemia/ HbE (the most common);
- iii. α -thalassaemia (HbH most clinically significant form) and
- iv. Abnormal Hbs (i.e. HbS, SC, SS, S β).

GUIDANCE FOR PATIENTS WITH THALASSAEMIA SYNDROMS

β homozygous (thalassaemia major), β -thalassaemia intermedia,
 β -thalassaemia/ HbE and HbH

RISK LEVELS

GROUP A – PATIENTS AT ‘MODERATE RISK’

- Are well transfused keeping pre transfusion haemoglobin levels between 9.5-10.0g/dl (in the last 3-4 years at least);
- Are well chelated with cardiac T2* >20 ms, LIC <7mg/gDw or ferritin <2000mg/L (in the last 3-4 years at least)⁶;
- Have no underlying co-morbidity⁷;
- Are not splenectomised⁸.

GROUP B – PATIENTS AT ‘HIGH RISK’

Any two or more of the following criteria:

- Have moderate diversions from international guidelines⁹ and keep pre-transfusion haemoglobin levels between 8.0-9.0g/dl (currently and in the last 2-3 years at least);
- Have chelation treatment challenges leading to moderate iron load as assessed by standardized MRI methods and serum ferritin levels (currently and in the last 2-3 years) as follows:

⁶ <https://b-s-h.org.uk/media/18229/iron-chelation-therapy-covid-version-2-150420.pdf>

⁷ <https://www.gov.uk/government/publications/coronavirus-covid-19-maintaining-educational-provision/guidance-for-schools-colleges-and-local-authorities-on-maintaining-educational-provision>

⁸ <https://www.gov.uk/government/publications/coronavirus-covid-19-maintaining-educational-provision/guidance-for-schools-colleges-and-local-authorities-on-maintaining-educational-provision>

⁹ TIF Guidelines for the Management of Transfusion Dependent Thalassaemia, 2014 (3rd edition)

- cardiac MRI T2* 10-15 ms¹⁰ and/or
- LIC 7-10 mg/d and /or
- serum ferritin between 2000 -3000 mg/L;
- ☑ Have one underlying co-morbidity including diabetes, pulmonary hypertension, endocrine, cardiac, respiratory disease¹¹;
- ☑ Are splenectomised and have another risk factor for complications as those described (e.g. diabetes)¹².

GROUP C – PATIENTS AT ‘HIGHEST RISK’

Any two or more of the following criteria:

- ☑ Are elderly more than 50 years’ old¹³;
- ☑ Have pre transfusion haemoglobin levels <7 mg/dl (in the last 2-3 years at least)
- ☑ Have chelation treatment challenges leading to high iron load as assessed by standardized MRI methods and serum ferritin levels (currently and in the last 2-3 years) as follows:
 - i. cardiac MRI T2* <10ms¹⁴
 - ii. LIC>11mg/g DW¹⁵
 - iii. serum ferritin >4000mg/L¹⁶
- ☑ Have one or more underlying co-morbidities including diabetes, pulmonary hypertension, endocrine, cardiac, respiratory disease¹⁷;

¹⁰ <https://b-s-h.org.uk/media/18229/iron-chelation-therapy-covid-version-2-150420.pdf>

¹¹ <https://www.gov.uk/government/publications/coronavirus-covid-19-maintaining-educational-provision/guidance-for-schools-colleges-and-local-authorities-on-maintaining-educational-provision>

¹² <https://www.gov.uk/government/publications/coronavirus-covid-19-maintaining-educational-provision/guidance-for-schools-colleges-and-local-authorities-on-maintaining-educational-provision>

¹³ <https://www.gov.uk/government/publications/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19#what-do-we-mean-by-extremely-vulnerable>

¹⁴ <https://www.gov.uk/government/publications/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19#what-do-we-mean-by-extremely-vulnerable>

¹⁵ <https://www.gov.uk/government/publications/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19#what-do-we-mean-by-extremely-vulnerable>

¹⁶ <https://www.gov.uk/government/publications/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19#what-do-we-mean-by-extremely-vulnerable>

¹⁷ <https://www.gov.uk/government/publications/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19#what-do-we-mean-by-extremely-vulnerable>

- ☑ Are splenectomised and have another one or more risk factor(s) for complications as the ones mentioned above (e.g. diabetes)¹⁸.

Although ageing may contribute to the development of co-morbidities, the age of the patient has not been included in the assessment of risk factors due to the fact that quality of care is the key determining factor of the presence or absence of co-morbidities, having very young patients in many parts of the developing world with significant co-morbidities subsequent to iron load and suboptimal care in general.

ASSOCIATION OF RISK LEVEL WITH SAFETY AT WORK / SCHOOL / EDUCATION

Thalassaemia patients are classified in risk levels according to their specific condition / circumstances, and hence not all fall within the same group of protective measures.

TIF made an effort to relate the different risk levels as mentioned above (Groups A, B and C) with the different levels of protective measures and by extension of 'relaxation' measures that could be taken at national level for patients with β –thalassaemia.

GROUP A - PATIENTS AT “MODERATE RISK”

The patients within this group could assume work/schooling/education without any other additional measures given that all national guidelines of distancing, hand washing and wearing mask are meticulously followed¹⁹ as every citizen without thalassaemia or any other underlying disease.

¹⁸ <https://www.gov.uk/government/publications/coronavirus-covid-19-maintaining-educational-provision/guidance-for-schools-colleges-and-local-authorities-on-maintaining-educational-provision>

¹⁹ <https://ukts.org/covid19faq/>

GROUP B - PATIENTS AT “HIGH RISK”

The patients within this group could assume work/schooling/education keeping all national guidelines of distancing, hand washing and wearing mask unless:

- their job involves very close contact with people (receptionists, shop assistants, education professionals e.g teachers etc) and/or
- they are treating/caring patients or vulnerable groups in general (e.g. nurses, health care professionals, are working in homes for the elderly, in hospital environments etc)

GROUP C - PATIENTS AT “HIGHEST RISK”

The patients within this group should absolutely refrain from any type of work/schooling/education activities and should REMAIN in a ‘shielded’ condition²⁰ without any level of relaxation measures until the pandemic is declared well over at country level.

In addition, these patients should continue keeping all national guidelines of distancing, hand washing and wearing mask at least 1-2 months after the pandemic is declared over at country level²¹.

Shielding means¹:

- Do not leave your house unless for extremely urgent and necessary needs.
- Do not attend any gatherings. This includes gatherings of friends and families in private spaces, for example, family homes, weddings and religious services.
- Strictly avoid contact with someone who is displaying symptoms of coronavirus (COVID-19). These symptoms include high temperature and/or new and continuous cough.

²⁰ <https://www.gov.uk/government/publications/coronavirus-covid-19-maintaining-educational-provision/guidance-for-schools-colleges-and-local-authorities-on-maintaining-educational-provision>

²¹ TIF’s Board of Directors opinion

ADVICE TO THE ACCIDENT & EMERGENCY DEPARTMENTS (A&E)

If a patient with β –thalassaemia is admitted to an A&E Department of a public or private hospital/clinic for any reason including COVID-19, the A&E doctors should:

- Contact immediately a thalassaemia treating physician to jointly assess the clinical condition of the admitted patient before discontinuing any medications unless admitted with fever²²;
- If the patient is admitted with fever, the A& E Department doctors should discontinue the iron chelation drugs and immediately contact the treating physician with the collaboration of whom the cause of the fever will be medically assessed²³. Desferrioxamine should be immediately discontinued if signs of bacterial superinfection exist and deferiprone should be discontinued because leukopenia is often observed during infections. However, there seems to be no need to discontinue deferasirox.

The contribution of the thalassaemia treating specialist cannot be underscored enough as there are circumstances in which stopping chelation in cardiac iron overload for example can be more harmful than beneficial.

GENERAL ADVICE FOR PATIENTS WITH THALASSAEMIA

The information below is an extract of the UK NHS recommendations²⁴ consequent to the advice and recommendations of the Red Blood Cells Units/Haemoglobin Disorders medical specialists. TIF provides these as they are publically available and are meant to only to help and support health care professionals around the world to

²² <https://b-s-h.org.uk/media/18229/iron-chelation-therapy-covid-version-2-150420.pdf>

²³ <https://b-s-h.org.uk/media/18229/iron-chelation-therapy-covid-version-2-150420.pdf>

²⁴ <https://b-s-h.org.uk/media/18229/iron-chelation-therapy-covid-version-2-150420.pdf>

have an idea and build perhaps their own protocols based on the country's health care facilities, knowledge and expertise on the management of hemoglobin disorders.

“For the patient who is isolated at home with presumed COVID-19 infection: The general recommendation for all transfusion-dependent thalassaemia major patients has been to interrupt iron chelation therapy if the patient is febrile until the fever has resolved and/or the cause of fever has been medically assessed by his/her treating specialist. There are circumstances under which stopping chelation in the context of fever can be harmful, particularly when cardiac iron is increased, so each case must be reviewed by their treating specialist.

All patients who are self-isolating due to symptoms or an infected household member will need to contact their treating specialist transfusion team and let them know they are in isolation so that transfusion therapy can be planned appropriately.

Patients with Cardiac T2 < 10 ms and proven or suspected Covid-19 infection:*

For the patient who is on Intravenous iron chelation therapy through a central venous access device or on oral iron chelation (monotherapy or combination therapy)

Daily contact with patients by specialist team either via email or telephone.

⇒ *If symptoms mild and patient not febrile advice to continue chelation and liaise with team on a daily basis.*

⇒ *If patient has fever > 37.8 oC then they should be admitted:*

- *Cardiac status must be assessed*
 - *Focused echo for LV function & TRjet Vmax (if any TR)*
 - *BNP if symptoms of breathlessness (a negative BNP rules out cardiac failure)*
 - *Baseline ECG*
- *Other causes of fever should be ruled out as per normal recommendations in TM such as infected lines, Gram negative bacteraemia or Yersinia infection.*

- *If fever is due to above then manage as per local protocols and guidelines for acutely unwell thalassaemia patients.*
- *Patients where other causes are excluded and are COVID-19 POSITIVE (this information may not be available immediately and may take several days) should continue on intravenous iron chelation with desferrioxamine and stop the oral iron chelation medication until the infection resolves.*
- *Careful monitoring is needed of patient's clinical state and the risk of cardiac decompensation is high if T2* is particularly low or if pre-existing low ejection fraction.*

Cardiac T2 > 10-20 ms and proven or suspect Covid-19 infection*

- ⇒ *If symptoms are mild and no fever then advise to continue iron chelation and daily contact with the team*
- ⇒ *If febrile they should present for face to face assessment at the hospital using the processes defined by the centre and possibly a COVID swab.*
- ⇒ *If no cardiac symptoms and cardiovascularly stable, then patients should aim to continue chelation therapy as soon as they have been assessed by their specialist centre and acute bacteraemic infection has been reasonably excluded*
- ⇒ *If patient develops palpitations, ankle swelling and worsening shortness of breath then to contact their team and attend hospital as a matter of urgency, be admitted and managed as per those patients with T2*.”*

HAEMOGLOBIN H DISEASE IN THE COVID-19 PANDEMIC

Haemoglobin H (HbH) disease is an alpha thalassaemia syndrome, with a very wide spectrum of clinical severity. In general, the mutations that are more frequently encountered in populations of Mediterranean origin cause an anaemia which is generally compatible with life without the need for blood transfusion support except for exceptional circumstances such as severe infections and pregnancy. It is classified as a non-transfusion dependent thalassaemia (NTDT) and as such **this group of**

patients should be included in the risk level of individuals that can return to work / school provided that national guidelines for protective measures of the general population are meticulously kept.

In contrast mutations in South East Asia often cause a more severe anaemia, and more often require blood transfusion to correct the anaemia.

Concerning the COVID-19 infection, the **major risk factor is the severity of anaemia in each individual patient**. Anaemia implies reduced oxygenation and so the **hypoxia induced by the respiratory complications of COVID-19, may be an added factor to worsen clinical outcomes**. This is of course a **largely theoretical possibility** in view of absence of any clinical evidence to date. During the viral infection careful **monitoring of haemoglobin levels** and **possible transfusion support** should be considered.

Patients with HbH are **in selected cases splenectomised**, mostly because of large spleen size and occasionally during an operation to deal with gallstones (again this is more common in the Asian varieties). Recommendation for these cases must be **in line with those recommendations provided for other haemoglobin disorders**, with the requirement for vaccinations and prophylactic penicillin either for young children on throughout life as per the country's policy

In the older age groups other co-morbidities should be considered, including cardiovascular disease. In any case **patients with HbH disease should be given a full clinical evaluation for any possible co-morbidities** and **accordingly to be classified for their risk level and consequently the protective measures** that should be recommended.

ADVICE ON BLOOD TRANSFUSION

THE RISK OF TRANSFUSION TRANSMITTED INFECTION IS CURRENTLY CONSIDERED BY EXPERTS TO BE ONLY THEORETICAL.

More information is available in TIF's 'Blood & COVID-19 Guide'²⁵.

In blood shortage it may be necessary to prioritize patients for transfusion or postpone less urgent transfusions²⁶. Treating physicians should review such decision according to circumstances and clinical condition of the patient. Every effort should be made at country level to empower and strengthen donation policies ensuring safe environment for donors, establish post donation follow ups along with the strengthened criteria for donor selection (already in place in most countries since the beginning of the pandemic). At the same time national blood establishment should ensure a 6-10 days, red blood cells reserves for the transfusion of these patients and other RBC needs.

In many countries, mainly of the developing world, it may be necessary to further strengthen patient management/clinical use of blood programmes and even revert, **hopefully very temporarily**, to family/friend donations to **avoid the situation of patients remaining not transfused or receiving whole blood** with all the anticipated negative consequences.

INFORMATION FOR TRANSPLANTED PATIENTS

Patients who have had Hematopoietic Stem Cell Transplantation (HSCT) or Gene Therapy/Editing or organ transplant, particularly within the last two years, are at increased risk of complications and should be advised to 'shield' because of reduced immunity²⁷. They should be given a 'Highest risk' scoring of vulnerability i.e. not returning to any type of work except electronic one, self-isolation and every effort should be made to be provided with home transfusion or in very 'isolated' spaces dedicated for the transfusion of the patients.

²⁵ <https://thalassaemia.org.cy/publications/tif-publications/blood-covid-19-2020/>

²⁶ <https://b-s-h.org.uk/media/18230/supporting-the-transfusion-needs-of-patients-with-inherited-red-cell-disorders-during-the-covid-19-pandemic-in-england-v15420.pdf>

²⁷ <https://b-s-h.org.uk/media/18244/hbp-hccs-response-to-covid-v9-200420.pdf>

TREATMENT OF COVID-19 IN PATIENTS WITH B-THALASSAEMIA

There are currently no specific recommendations for patients with Thalassemia major / intermedia for the therapy of COVID-19. For patients with thalassemia intermedia in particular, it should be noted in connection with the potential option of therapy with hydroxychloroquine that in many regions of origin, glucose-6-phosphate dehydrogenase deficiency with the associated risk of drug-induced haemolytic crises may occur frequently and independently²⁸. This enzyme deficiency may also have been co- inherited with thalassemia.

One particular endocrine complication, is underactivity of the adrenal glands (adrenal hypofunction), which may not have been diagnosed. In the presence of a serious infection, however, the ability to limit the effects of the infection may be compromised. In dealing with a thalassaemia patient infected by the virus this possibility should be taken into consideration and although the possibility of provision of low-dose glycocorticoid supplementation may be considered to address it, it must be taken into account that corticosteroids may slow down clearance of viral RNA from respiratory tract in SAR-CoV and MERS-CoV infections and subsequently increase complications²⁹.

SPLENECTOMISED PATIENTS

The extract below from British Society of Haematology “Guidance on shielding for Children and Adults with splenectomy or splenic dysfunction during the COVID-19 pandemic”³⁰ demonstrates the importance of this topic in the care of haemoglobin disorders.

²⁸ Motta I et al, 2020. SARS-CoV-2 infection in beta thalassemia: preliminary data from the Italian experience. <https://onlinelibrary.wiley.com/doi/epdf/10.1002/ajh.25840>

²⁹ COVID-19 & Haemoglobin Disorders: A TIF publications <https://thalassaemia.org.cy/el/tif-publications/covid-19-pandemic-haemoglobin-disorders-2020/>

³⁰ https://b-s-h.org.uk/media/18292/covid19-bsh-guidance-on-splenectomy-v2-final-6-may2020_.pdf

TIF acknowledges that similar guidance may be available in other countries, tailored to individual national expertise, experience and situations but are not however readily available in English at present. Hence the UK guidelines serve as a reference on the topic of splenectomy.

“Guidelines recommend that all asplenic patients, irrespective of underlying cause, should have been immunised with certain specific vaccines – pneumococcal polysaccharide and conjugate, Hib conjugate and meningococcal – and be on long-term prophylactic anti-microbial therapy as appropriate (Davies et al 2011, Rubin and Schaffner 2014).

Asplenic/hyposplenic patients are also advised to receive influenza immunisation due to the increased risk of secondary bacterial infection after contracting influenza. Patients normally invited for annual flu immunisation are currently defined as “vulnerable”, being at moderate risk of Covid-19 complications, and advised to maintain strict social distancing. However, the need for influenza immunisation is not, in itself, an indication of a higher risk of Covid-19 and therefore, not an indication for shielding in the asplenic/ hyposplenic patient.

Based on knowledge of the immunological functions of the spleen, there is no evidence that the lack of a spleen or part of a spleen or a non -functioning spleen on its own renders patients at higher risk of Covid-19. Recommendations for shielding will therefore depend in the underlying cause for splenectomy or asplenia and any associated comorbidities and treatments. Further guidance is available from the British Society for Haematology in relation to the management of different underlying conditions which may be associated with splenectomy or functional asplenia (see below).

However, since fever could indicate bacterial as well as viral infection, all patients should be instructed to seek urgently medical advice their national authorities if they develop a new fever, stating that have an absent or non -functioning spleen. Consideration should be given to the presence of bacterial infection, particularly with capsulated pathogens.

Recommendations applying to all patients

- *Patients should ensure they are up to date with their vaccinations*
- *Patients taking regular prophylactic antibiotics should be encouraged to continue*
- *Those who are not taking antibiotics should have a supply at home to take if unwell and instructed to do so by a clinician*
- *All patients reporting a new fever should be evaluated for bacterial as well as viral infection*

Haemoglobinopathy/inherited red cell disorders

Sickle Cell Disease (SCD), of all genotypes, is associated with hyposplenism. Guidance from the Haemoglobinopathy Coordinating Centres (HCC) recommends which patients with SCD and Thalassaemia are considered clinically extremely vulnerable and need to shield. The initial advice was that all patients with SCD and high risk patients with Thalassaemia and other inherited red cell anaemias should shield. This latter group included patients with Thalassaemia or other inherited red cell disorders with splenectomy plus significant iron overload and/or comorbidities e.g. diabetes, cardiac disease This advice is being updated regularly based on accumulated data of outcomes in SCD and Thalassaemia with Covid-19. (<https://b-s-h.org.uk/media/18244/hbp-hccs-response-to-covid-v9-200420.pdf>).

Based on this data and following the initial period of shielding, due to end in June 2020, it is proposed that some of the patients will be classified as 'clinically vulnerable instead of 'clinically extremely vulnerable' and will no longer be recommended to continue shielding. after this time.

Patients who do not require shielding (providing no other indication for shielding)

All other patients. This will include:

- *Splenectomy for trauma*
- *Thalassaemia or other inherited red cell disorders with splenectomy but without significant iron overload or comorbidities*
- *Splenectomy for autoimmune disorders but not currently taking immunosuppressive treatment and not on SPL due to underlying disease."*

Thromboembolic events: patients with thalassaemia major particularly non transfusion dependent thalassaemias, are at higher risk of thrombosis or cerebrovascular disease, especially adult and splenectomised patients, and in addition with pulmonary hypertension; LIC \geq 5mg/g DW, or Ferritin \geq 800mg/ms. In such an event: Prophylactic intervention with anticoagulant or antiaggregants, aspirin and the use of transfusion therapy – thrombosis prophylaxis with LMWH are recommended for example by the German Society of Thrombosis and Haemostasis Research e.V. (GTH) for adult patients with COVID-19 and inpatient treated adolescent patients with COVID-19³¹.

³¹ <https://www.onkopedia.com/de/onkopedia/guidelines/coronavirus-infektion-covid-19-bei-patienten-mit-blut-und-krebserkrankungen/@@guideline/html/index.html?chapter=6.2.63#ID0EFRAI>

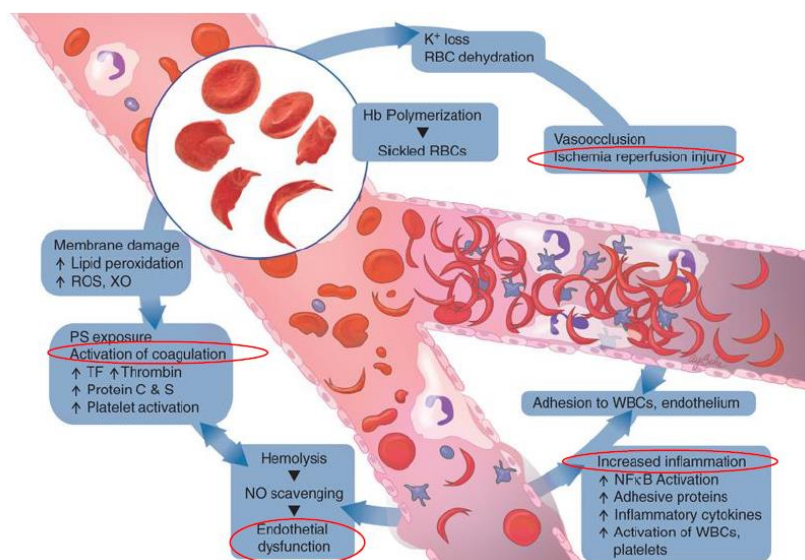
GUIDANCE FOR PATIENTS WITH SICKLE CELL DISEASE (SCD)

WHY MORE SUSCEPTIBLE TO SERIOUS COVID-19 DISORDER?

The greatest majority of individuals with Sickle Cell Disease (SCD) syndromes, if not all, in almost every county worldwide are included amongst the vulnerable, at “highest risk” groups of patients³²:

Patients with SCD often have underlying cardiopulmonary co-morbidities that may predispose them to poor outcomes if they become infected with a respiratory virus like SARS-CoV-2. In addition, they are all at increased risk of bacterial infections particularly due to functional asplenia. Given the overlap in presenting symptoms between COVID-19 and other diagnosis, patients are being advised to contact the soonest possible, if they develop symptoms, their treating specialist. Any delay, may delay access to life saving antibiotics and other care.

The pathophysiology pathway of SCD clearly provides the possible reasons for classifying patients with this disorder as vulnerable and at highest risk to a more severe COVID-19 infection.



Source: K. Kaushansky, M.A. Lichtman, J.T. Prchal, M.M. Levi, O.W. Press, L.J. Burns, M. Caligiuri: Williams Hematology, 9th edition www.accessmedicine.com Copyright © McGraw-Hill Education. All rights reserved.

³² <https://www.gov.uk/government/publications/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19/guidance-on-shielding-and-protecting-extremely-vulnerable-persons-from-covid-19#what-do-we-mean-by-extremely-vulnerable>

A major difference between patients with β -thalassaemia and those with SCD is that the latter group does not have a regular follow up in Red Blood Cells Units in the context of their management despite the recommendations of medical experts in the field to do so. **This particularly happens in the developing part of the world. In this context, patients with SCD both on account of their underlying genetic disease and its pathophysiology and the irregular monitoring of their condition and complications, are at 'highest risk' amongst the vulnerable groups of patients in every country.**

CLINICAL KEY ELEMENTS OF SCD INCLUDE:

- ☑ Functional asplenia – splenectomised with increased risk of severe bacterial infection
- ☑ Acute events i.e. vaso-occlusive crisis or fever
- ☑ Acute chest syndrome- 2nd most frequent clinical complication and reason for hospital admission

COVID-19 & SCD

“Progressive endothelial inflammatory syndrome involving the microvascular bed of the lungs, the brain and other vital organs”

- Lung disorder: bilateral pneumonia
- Systemic inflammatory response – Cytokine-release syndrome (IL 6, IL1 etc)
- Diffuse thromboembolism
- Increasing evidence of other organ involvement that many lead to multiple organ failure

MANAGEMENT OF SCD WITH OR WITHOUT COVID-19 DURING THE PANDEMIC

MANAGEMENT OF PATIENTS WITH SCD & POSSIBLE COVID-19 INFECTIONS

- ✔ It is essential that fever in patients with haemoglobinopathies in general and more particular in SCD is not presumed to be due to COVID-19 infection as these patients are hyposplenic and therefore also at high risk of infections from other causes³³.

- ✔ Patients should urgently let their treating specialist teams know if they have symptoms of COVID-19 (fever, cough etc) which they are managing at home or as soon as they are admitted to any hospital.

- ✔ Patients with a fever of $>37.8^{\circ}\text{C}$ require an immediate clinical review, either virtually or in person by their treating specialist or attend the Accident & Emergency Department (A&E) without delay if the treating specialist is not available or accessible for urgent assessment Standard of care for managing fever in SCD patients should be followed wherever the patient presents himself/herself with fever including clinical and laboratory examination e.g. blood cultures and prompt provision of antibiotic therapy³⁴.

- ✔ The Emergency Department should test patients for COVID-19³⁵ presenting symptoms related to COVID-19: fever, cough, pain in the chest, difficulty in breathing in adults and unusual rash in the case of children.

³³ <https://b-s-h.org.uk/media/18244/hbp-hccs-response-to-covid-v9-200420.pdf>

³⁴ <https://b-s-h.org.uk/media/18244/hbp-hccs-response-to-covid-v9-200420.pdf>

³⁵ <https://b-s-h.org.uk/media/18244/hbp-hccs-response-to-covid-v9-200420.pdf>

- ✔ The Emergency Department/admitting medical teams should contact the haemoglobinopathy teams as soon as a patient with SCD presents at the A&E with fever or other COVID-19 symptoms³⁶.
- ✔ If patients are discharged to self-isolate they should be given additional antibiotics and close phone follow up should be arranged by the haemoglobinopathy expert team who should be advising very promptly the patients to present to the clinic or hospital if they have worsening symptoms³⁷.
- ✔ Infants with SCD with fever or shortness of breath should follow standard procedure according to their treatment protocols/guidelines and if treating specialist is not directly available, the parent(s) should visit, without any delay, the A& E department, the staff of which will provide emergency support and will need to contact the infant's treating specialist i.e. SCD paediatric specialist³⁸.

PATIENTS WITH SCD ADMITTED TO HOSPITAL WITH COVID-19 PROVEN OR SUSPECT INFECTION (FEVER, RESPIRATORY SYMPTOMS)

- ✔ If the above symptoms occur, pulmonary images should be carried out as soon as possible³⁹. CT imaging is necessary as it is more informative than a simple CXR.
- ✔ If there are radiological changes (some providers repeat CXR 48 hours post admission if test is positive or result not back yet) or signs of hypoxemia, a single transfusion is carried out (if necessary with prior bloodletting in the event that haemoglobin value has not already decreased due to an increase in haemolysis).
- ✔ In the event of clinical deterioration, an exchange transfusion is performed (target haemoglobin S level <30%)⁴⁰.

³⁶ <https://b-s-h.org.uk/media/18244/hbp-hccs-response-to-covid-v9-200420.pdf>

³⁷ <https://b-s-h.org.uk/media/18244/hbp-hccs-response-to-covid-v9-200420.pdf>

³⁸ <https://b-s-h.org.uk/media/18244/hbp-hccs-response-to-covid-v9-200420.pdf>

³⁹ <https://www.hematology.org/covid-19/covid-19-and-sickle-cell-disease>

⁴⁰ <https://b-s-h.org.uk/media/18244/hbp-hccs-response-to-covid-v9-200420.pdf>

SICKLE CELL DISEASE AND ACUTE CHEST SYNDROME: The symptoms of acute chest syndrome and COVID19 overlap and infection with COVID-19 may increase the risk of acute chest syndrome. Clinicians should be extra vigilant for this complication and should treat patients fulfilling the criteria for acute chest syndrome (respiratory signs and symptoms, abnormal Chest X-Ray) as per national/international guidance⁴¹. Providers should actively monitor for and have a low threshold for imaging to investigate for localized infiltrates consistent with pneumonia or acute chest syndrome versus the more diffuse glass appearance commonly seen with COVID-19⁴².

This will include **treatment with top up or exchange transfusion**. Clinicians should consider **early top up transfusion** if there are clinical concerns (e.g desaturation on exercise) and/or rapidly evolving chest involvement. There may be an increased need for **emergency top up** and **exchange transfusion** during this time. Services should develop plans for how they can provide emergency apheresis capacity⁴³.

MANAGEMENT OF ACS IN SCD PATIENTS INFECTED WITH COVID-19 INCLUDES:

- ☑ Early exchange transfusion
- ☑ Broad spectrum antibiotics – include MRSA coverage, atypicals, pneumococcus
- ☑ Plasmapheresis may be of some to even great benefit
- ☑ Consult Paediatric or Adult Pulmonary as well as Haematology specialist accordingly

PATIENTS WITH SCD PRESENTING TO HOSPITAL WITH COVID-19 RELATED SYMPTOMS⁴⁴

⁴¹ <https://b-s-h.org.uk/media/18244/hbp-hccs-response-to-covid-v9-200420.pdf>

⁴² <https://b-s-h.org.uk/media/18244/hbp-hccs-response-to-covid-v9-200420.pdf>

⁴³ <https://b-s-h.org.uk/media/18244/hbp-hccs-response-to-covid-v9-200420.pdf>

⁴⁴ <https://b-s-h.org.uk/media/18244/hbp-hccs-response-to-covid-v9-200420.pdf>

- ☑ In case patients present for management of acute pain, they should be encouraged to treat pain as per their standard care protocol but to contact their clinical specialist(s) in case they have a fever or respiratory symptoms.

- ☑ Patients should be encouraged to attend the A&E Department if any of the following occur:
 - Uncontrolled pain >7/10 despite the use of usual home analgesia
 - Respiratory distress (new shortness of breath or increased breathlessness compared to baseline particularly at rest or on minimal exertion) +/- chest pain
 - Persistent fever >38°C
 - Severe headache, confusion or neurological changes.

CLINICIANS SHOULD BE AWARE THAT PATIENTS WITH SCD MAY PRESENT WITH THESE SYMPTOMS IN THE ABSENCE OF COVID-19 AND USUAL PATHWAYS FOR INVESTIGATION AND MANAGEMENT SHOULD BE FOLLOWED ALWAYS IN COLLABORATION WITH THE RED BLOOD CELLS/HAEMOGLOBIN DISORDERS MEDICAL SPECIALISTS.

SOME PRACTICAL ADVICE FOR OUTPATIENT CARE OF ASYMPTOMATIC PATIENTS

- ☑ Move to virtual consultations where possible.

- ☑ Postpone non-essential investigations.

- ☑ Patients on hydroxycarbamide or iron chelation will need regular monitoring to continue but this could be done virtually and on an extended schedule (maximum interval 4-6 monthly for hydroxycarbamide).

- ☑ Offsite phlebotomy services should be utilised if possible.

- ✔ Home delivery pharmacy services should be utilised if possible Patients should not attend outpatients or day unit if they have temperature/respiratory/coryzal symptoms.
- ✔ Teams should set up a generic phone advice and generic email for patient queries, which will be manned by clinical staff.
- ✔ **HYDROXYCARBAMIDE:** There is no evidence that being on hydroxycarbamide would increase risk of COVID-19 as long as there is no related myelosuppression. Patients should be urged to remain on their usual hydroxycarbamide dosages to maintain good health and avoid hospital admissions. It may be advisable to avoid routinely starting or dose escalating hydroxycarbamide to reduce need for repeated phlebotomy and hospital visits to minimize the risk of infection. For stable patients it is reasonable to extend the interval between monitoring blood tests⁴⁵.
- ✔ **TRANS-CRANIAL DOPPLER (TCD) SCREENING:** These may also need to be postponed but services should consider how they can continue to provide this for essential groups. Patients with HbSS and SBoThal needing their first TCD and patients with previous conditional or first abnormal TCD should be prioritised. TCDs in younger patients (especially those <10 years) should also be prioritised unless they are already on transfusion and stable, in which case their scans can be delayed⁴⁶. Additional advice to clinicians is currently being developed. Clinicians should discuss with their vascular scientists about how this service can be provided. Clinicians should consider changing patients who are currently on transfusion for primary stroke prevention to hydroxycarbamide as per the TWITCH trial protocol which provides convincing evidence that children with SCA and abnormal TCD measures receiving regular blood transfusion therapy for at least a year, can be transitioned to hydroxycarbamide therapy at maximum tolerated dose over a course of approximately 6 month⁴⁷. This makes hydroxycarbamide at maximum tolerated dose a viable option to no regular blood transfusion for children

⁴⁵ COVID-19 & Haemoglobin Disorders: A TIF publications <https://thalassaemia.org.cy/el/tif-publications/covid-19-pandemic-haemoglobin-disorders-2020/>

⁴⁶ <https://b-s-h.org.uk/media/18244/hbp-hccs-response-to-covid-v9-200420.pdf>

⁴⁷ DeBaun, M. 2020. Initiating adjunct low dose-hydroxyurea therapy for stroke prevention in children with SCA during the COVID-19 pandemic, Blood. <https://ashpublications.org/blood/article-lookup/doi/10.1182/blood.2020005992>

with abnormal TCD measurements. Preliminary data also indicate that low dose of hydroxycarbamide therapy decreases the expected incidences and rate of acute vaso-occlusive pain and ACS events in both children and adults⁴⁸. So perhaps in the absence of blood transfusion therapy in period of blood shortages and initiation of hydroxycarbamide may be of clinical benefit with negligible risks (as compared to no blood transfusion)⁴⁹.

- ☑ **IBUPROFEN:** Concerns have been raised about the role of ibuprofen (perhaps not limited to ibuprofen but also to every anti-inflammatory drug with the same mechanism of action) in this condition. In febrile patients with suspected Covid-19 infection other agents should be considered in preference to ibuprofen if possible until further evidence is available. Please refer to PHE/NHSE sites for most up to date advice.

All treating specialists should continuously keep themselves updated on the latest information, as new data constantly emerge. SARS-CoV-2 is a new virus and a new infection with many still unknown effects. Therefore global collaboration and exchange of knowledge are essential in this fight.

ASPLENIA / HYPOSPLENIA

RISK OF SEVERE COURSE OF COVID-19

To date there have been no reports of severe course of COVID-19 in asplenia / hyposplenia. Extrapolating from experience in the context of influenza, an increased risk for or a severe course of bacterial pulmonary superinfections, in particular through pneumococci, is conceivable⁵⁰.

⁴⁸ DeBaun, M. 2020. Initiating adjunct low dose-hydroxyurea therapy for stroke prevention in children with SCA during the COVID-19 pandemic, Blood. <https://ashpublications.org/blood/article-lookup/doi/10.1182/blood.2020005992>

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⁵⁰ <https://www.onkopedia.com/de/onkopedia/guidelines/coronavirus-infektion-covid-19-bei-patienten-mit-blut-und-krebserkrankungen/@@guideline/html/index.html?chapter=6.2.63#ID0EFRAI>

ASSISTANCE IN THE FACE OF THE THREAT FROM COVID-19

Vaccination protection against pneumococci is particularly important (sequential vaccination with Prevenar-13® and Pneumovax®)⁵¹.

CHANGE OF SUPERVISION WHEN PROOF OF SARS-COV-2

If bacterial superinfection is suspected, a pneumococcal and haemophilus-active antibiotic should be used. Ampicillin / Sulbactam 3x3g / d iv is the treatment of choice for suspected bacterial pneumonia. Close clinical follow-up, if necessary under inpatient conditions, is recommended⁵².

Azithromycin should be the first antibiotic prescribed for patients hospitalized for COVID-19, in the absence of bacterial infection by a microorganism outside its spectrum.

Penicillin prophylaxis for life (beyond the age of 5) in splenectomized/ hyposplenic patients is a policy that has different adoption policies in different countries.

SPLENECTOMISED PATIENTS

The extract below from British Society of Haematology "Guidance on shielding for Children and Adults with splenectomy or splenic dysfunction during the COVID-19 pandemic"⁵³ demonstrates the importance of this topic in the care of haemoglobin disorders.

⁵¹ https://www.onkopedia.com/de/onkopedia/guidelines/coronavirus-infektion-covid-19-bei-patienten-mit-blut-und-krebserkrankungen/@_@guideline/html/index.html?chapter=6.2.63#ID0EFRAI

⁵² https://www.onkopedia.com/de/onkopedia/guidelines/coronavirus-infektion-covid-19-bei-patienten-mit-blut-und-krebserkrankungen/@_@guideline/html/index.html?chapter=6.2.63#ID0EFRAI

⁵³ https://b-s-h.org.uk/media/18292/covid19-bsh-guidance-on-splenectomy-v2-final-6-may2020_.pdf

TIF acknowledges that similar guidance may be available in other countries, tailored to individual national expertise, experience and situations but are not however readily available in English at present. Hence the UK guidelines serve as a reference on the topic of splenectomy.

“Guidelines recommend that all asplenic patients , irrespective of underlying cause, should have been immunised with certain specific vaccines – pneumococcal polysaccharide and conjugate, Hib conjugate and meningococcal – and be on long-term prophylactic anti-microbial therapy as appropriate (Davies et al 2011, Rubin and Schaffner 2014).

Asplenic/hyposplenic patients are also advised to receive influenza immunisation due to the increased risk of secondary bacterial infection after contracting influenza. Patients normally invited for annual flu immunisation are currently defined as “vulnerable”, being at moderate risk of Covid-19 complications, and advised to maintain strict social distancing. However, the need for influenza immunisation is not, in itself, an indication of a higher risk of Covid-19 and therefore, not an indication for shielding in the asplenic/ hyposplenic patient.

Based on knowledge of the immunological functions of the spleen, there is no evidence that the lack of a spleen or part of a spleen or a non -functioning spleen on its own renders patients at higher risk of Covid-19. Recommendations for shielding will therefore depend in the underlying cause for splenectomy or asplenia and any associated comorbidities and treatments. Further guidance is available from the British Society for Haematology in relation to the management of different underlying conditions which may be associated with splenectomy or functional asplenia (see below).

However, since fever could indicate bacterial as well as viral infection, all patients should be instructed to seek urgently medical advice their national authorities if they develop a new fever, stating that have an absent or non -functioning spleen. Consideration should be given to the presence of bacterial infection, particularly with capsulated pathogens.

Recommendations applying to all patients

- *Patients should ensure they are up to date with their vaccinations*
- *Patients taking regular prophylactic antibiotics should be encouraged to continue*
- *Those who are not taking antibiotics should have a supply at home to take if unwell and instructed to do so by a clinician*
- *All patients reporting a new fever should be evaluated for bacterial as well as viral infection*

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ADVICE ON BLOOD TRANSFUSION

THE RISK OF TRANSFUSION TRANSMITTED INFECTION IS CURRENTLY CONSIDERED BY EXPERTS TO BE ONLY THEORETICAL.

More information is available in TIF's 'Blood & COVID-19 Guide'⁵⁵.

Exchange transfusions: There is no evidence that automated exchange transfusions are aerosol generating⁵⁶.

Manual exchange transfusions should be performed as a closed procedure, in which case it is not thought to be an aerosol generating procedure and the risk of blood spillage is low and in this context standard protection measures should be used. If a closed system is not being used, then there may be a risk of blood spillage and PPE level measures may be necessary⁵⁷.

⁵⁴ https://www.onkopedia.com/de/onkopedia/guidelines/coronavirus-infektion-covid-19-bei-patienten-mit-blut-und-krebserkrankungen/@_@guideline/html/index.html?chapter=6.2.63#ID0EFRAI

⁵⁵ <https://thalassaemia.org.cy/publications/tif-publications/blood-covid-19-2020/>

⁵⁶ <https://b-s-h.org.uk/media/18230/supporting-the-transfusion-needs-of-patients-with-inherited-red-cell-disorders-during-the-covid-19-pandemic-in-england-v15420.pdf>

⁵⁷ <https://b-s-h.org.uk/media/18230/supporting-the-transfusion-needs-of-patients-with-inherited-red-cell-disorders-during-the-covid-19-pandemic-in-england-v15420.pdf>

Blood supply: All national blood establishments are working to maintain adequate blood supplies. Information or supplies through national inventories should be available electronically and every effort should be made to ensure at least 6-10 days, red blood cells reserves at all times is ensured to address the needs for the RBC transfusion of these patients and certainly other major needs for RBC transfusions.

TIF COVID-19 HELP DESK & COMMUNICATION LINE

To facilitate contact with our members and patients, we have created a Help Desk & Communication Line, specifically for issues concerning the COVID-19 outbreak!

YOU CAN REACH US DIRECTLY AT TIF-COVID19@THALASSAEMIA.ORG.CY