SCD/Thalassemia and COVID-19: Possible Risks and a Proposal for a Patient Pathway During the Pandemic

COVID-19 Webinar Series: Session 03 | 16 April 2020 | 17:00 CEST

The content discussed during this webinar is based on the personal experiences & opinions of the speakers. No general, evidence-based guidance can be derived from this discussion.
Sharing experiences and insights on SCD/Thalassemia and COVID-19: Possible Risks and Proposed Patient Pathway During the Pandemic

Speakers

• Dr Raffaella Colombatti
  Department of Women's and Children's Health SDB, University of Padova, Italy

• Prof Maria-Domenica Cappellini
  Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Italy

• Dr Androulla Eleftheriou
  Executive Director, Thalassaemia International Federation, Cyprus

Moderator

• Dr. Francesco Cerisoli, European Hematology Association
Thalassemia Syndromes

Maria Domenica Cappellini

University of Milan, Medical School

Italy
Thalassemia Syndromes

• Thalassemia Syndromes are an heterogeneous group of autosomal recessive inherited disorders caused by reduced or absent hemoglobin chain synthesis, leading to ineffective erythropoiesis and subsequent chronic anemia

• According to WHO, Thalassemias represent one of the most frequent causes of anemia, affecting more than 7% of the world population
Evolving global burden due to migration

Predominance in low- or middle-income countries stretching from sub-Saharan Africa, through the Mediterranean region and the Middle East, to South and Southeast Asia.

Recent global population movements have also led to increasing incidences in areas of the world previously relatively unaffected by these conditions such as Europe and the US.

Transfusion requirement is commonly used to distinguish phenotypes

Non-transfusion-dependent thalassemia (NTDT)
- β-thalassaemia intermedia
- Mild/moderate HbE/β-thalassemia
- HbH disease (α-thalassemia intermedia)

- Transfusions seldom required
- Occasional transfusions required (e.g. surgery, pregnancy, infection)
- Intermittent transfusions required (e.g. poor growth and development, specific morbidities)
- Regular, lifelong transfusions required for survival

- Transfusions not required
- α-thalassemia trait
- β-thalassemia minor

Transfusion-dependent thalassemia (TDT)
- β-thalassemia major
- Severe HbE/β-thalassemia
- Hb Barts hydrops (α-thalassemia major)

Complications of NTDT vs. β-Thalassaemia Major

β-Thalassaemia major (regularly transfused) vs. NTDT

- **Silent cerebral ischaemia**
- **Hypothyroidism**
- **Hypoparathyroidism**
- **Hypogonadism**
- **Diabetes mellitus**
- **Hepatic failure**
- **Viral hepatitis**
- **Osteoporosis**
- **Splenomegaly**
- **Gallstones** (cholelithiasis)
- **Hepatic fibrosis, cirrhosis and cancer**
- **Extramedullary haemopoietic pseudotumours**
- **Right-sided heart failure**
- **Pulmonary hypertension**
- **Venous thrombosis**
- **Leg ulcers**

Are patients with thalassemia more susceptible to serious COVID-19 disease?

- Patients with pre-existent chronic morbidities are likely to be more severely affected by SARS-Cov2 infection, but no data are available regarding Thalassemic Syndromes

- Patients with thalassemia, particularly those of the older age group, were frequently splenectomized and this renders them vulnerable to bacterial infections and can trigger serious and life threatening sepsis. Splenectomy is not known to increase the risk of viral infection or severe viral illness

- Blood transfusion: to date, there is no evidence that COVID-19 may be transmitted through blood
A small cohort of Italian patients followed in the northern part of Italy, where the pandemic has been the most widespread, experienced relatively mild to moderate COVID-19 disease.

The number of infected thalassemia patients was lower than expected, likely due to earlier and more vigilant self-isolation compared to the general population. Only one NTDT patient was reported.

All the patients had thalassemia associated comorbidities.

72% of the patients were splenectomized. Splenectomy did not affect the clinical course.

The likely source of infection has been detected in 64% of cases.
Italian experience based on SITE network survey

Updated April 4°,2020

• 53.5% of the patients were hospitalized but no one required ICU

• The patient with more severe symptoms and requiring a more intensive ventilation support with continuous positive airway pressure (CPAP) has a history of diffuse large B-cell lymphoma treated with chemotherapy in 2019 currently in complete remission

• Among the patients admitted to the hospital only three received specific treatment for COVID-19: one hydroxychloroquine (HCQ) alone, one HCQ plus anakinra, and one HCQ plus ritonavir/darunavir

• No increase in blood requirement was observed
Measures implemented by Italian Centres

• Since February 2020, we rapidly reorganized the activities, postponing the non-essential ones, and providing time and staff to help the front line

• At the beginning of the pandemic all our Thalassemia and sickle cell disease patients had been advised by phone calls, email, or directly at the center to follow the containment measures. (*SITE communication* [http://www.site-italia.org/2020/covid-19.php])
Measures implemented by Italian Centres

• We offered patients a safe track at the hospital to receive their life-saving treatment in COVID-19 free areas, with healthcare personnel wearing personal protective equipment

• To prevent access of symptomatic patients, the hospital door filter and the temperature check, have been preceded and followed by our phone and ward access triage

• Symptomatic patients were isolated, tested, and if positive, they received the care and transfusion in a dedicated COVID-19 area.
TIF’s response to the COVID-19 pandemic: Adequacy of blood supplies

Responses from Patients (TIF CAB members) through webinars & written communication:

• Shortage of blood in 75% across 62 countries members of TIF:
  • 58% report severe shortages; pre-transfusion Hb falling <7.5 g/dl
  • 35% report moderate to severe shortages; 1 - 2 g/dl drop in pre-transfusion Hb
  • 7% report adequacy of blood

• Ways identified to combat shortages as reported by TIF CAB members:
  • Return to family/friends donation practices
  • Whole blood transfusion (rare but reported)
  • Older blood transfusions (>28 days)

Impressive responses of **solidarity & altruism** by citizens of some countries for increasing blood supplies! **Result:** More supplies of blood for TDT patients comparing to before COVID-19 outbreak!
TIF’s response to the COVID-19 pandemic: National responses to blood safety & adequacy – the patients perspective

Responses from Patients (TIF CAB members) through webinars & written communication:

• Most countries in Europe and North America have:
  • Reformed their Blood Donors questionnaire
  • Have developed a post-donation questionnaire
  • Strengthened haemovigilance and patient management programmes (clinical use of blood)
  • Reforming the strategy of transfusion interval: reducing the amount of blood to thalassaemia patients from 2 units to 1 unit during any transfusion but made arrangements for more frequent transfusions (e.g. 1 a week).
    • Important in order to limit the time spent in the clinic and to control blood supplies whilst safeguarding that all TDT patients will be able to get their transfusion
Reported to TIF cases of Thalassaemia patients infected with SARS-COV-2

Clinical Symptoms reported:
✓ Severe Liver Iron Concentration & past HCV infection
✓ Pulmonary Hypertension
✓ Mild myocardial & mild liver iron
✓ Splenectomy
✓ Diabetes
✓ Underlying history of ulcerative colitis & lung clots

On admission:
46/51 presented mild to moderate respiratory symptoms & a temperature <40°C

5/51 had radiological and clinical evidence of severe respiratory symptoms, a temperature >40°C (in need of oxygen & drug therapy - antibiotic cover) & required hospitalisation

2 of 5 were hospitalized & discharged without sequelae 7 – 10 days after admission

3 of 5 have passed away, 5 and 15 days post-hospitalization

Data correct to-date: 16/04/2020

Number of patients: 51
Diagnosis: TDT
Location: Cyprus, Italy, UK, France, Turkey, Iran, Pakistan, Indonesia
Sickle Cell Disease

Raffaella Colombatti

Clinic of Pediatric Hematology Oncology, Department of Woman’s and Child’s Health, Azienda Ospedale-Università di Padova

Italy
Sickle Cell Disease

• Genetic Disorders of Hemoglobin (HbSS, HbSB°HbSC, HBSB+...) with haemolytic anemia, vaso-occlusion, risk of infection but with phenotypic diversity

• Chronic Disorder with organ complications (brain, kidney, lung...) since childhood and need of chronic routine health care and treatments (drugs, RBC transfusions)

• Acute Manifestations that can be unpredictable and severe (sepsis, vaso-occlusive painful crisis, acute chest syndrome, stroke...)
What is specifically known about Sickle Cell Disease and COVID-19 disease

- 4 published cases of Acute Chest Syndrome due to COVID-19 in France, the Netherlands and the USA
  *Nur et al AJH 2020, De Luna G et al AJH 2020, Beerkens et al AJH 2020*
  - VOC as a trigger of ACS
  - COVID19 ACS (while infectious causes are less common in adults)
  - Criteria for COVID19 infection screening – diagnosis – resolution
  - COVID19 treatment in SCD

- Unpublished information comes from Expert Discussions – Experience sharing across continents through networks and scientific societies
Are patients with SCD more susceptible to serious COVID-19 disease?

1. SCD

Pathophysiology
2. SCD Clinical Key elements

- Functional asplenia – splenectomized with increased risk of severe bacterial infections
- Acute events – i.e. Vaso-occlusive crisis or fever - with access to health care facilities
- Acute Chest Syndrome is 2\textsuperscript{nd} most frequent clinical complication and reason for admission
3. COVID 19:

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

Ciceri et al Crit Care Resuscit 2020

- Lung disorder: bilateral pneumonia
- Systemic Inflammatory response – Cytokine Release Syndrome (IL 6, IL 1..)
- Diffuse Thromboembolism
- Increasing evidence of other organ involvement

Shi et al 2020, Dolhnikoff et al JTH 2020, Terpos et al AJH 2020
SCD during COVID pandemic: What has been done so far?

1. Patients’ protection and Educational Material: stimulate application of measures to limit exposure


https://www.sichelzellkrankheit.info/

https://eurobloodnet.eu/covid-19/
2. Reorganization of Pediatric and Adult SCD Services

- Enhanced use of Telemedicine and Teleconsultation
- Reduce access for on site visits in hematology/pediatric hematology units (safe transportation provided)
- Delay of non urgent transfusions if necessary (NOT for stroke prevention in children)
- Dedicated pathways of access in the units with clinical screening before entrance (TC measurement and symptoms assessment), distancing in waiting rooms
- Coordination with local ERs and COVID teams/services to establish adequate pathways
- Focus on continuation of drug supply (home delivery) or alternate access for drug procurement
3. Patients’ Management: SCD + COVID

Example of an Adult Network in times of COVID pandemic in Europe

- hotline telephone/telemedicine monitoring system both for VOC and for patients with suspected COVID or confirmed COVID
  
  - 500 calls

- home care network with nurses 3 times a day (3 Home health providers)
  
  - 70 visits

- 2 different visits circuits for VOC or COVID + patients (dedicated rooms); patients are brought by taxis and ambulances with trained staff

- systematic screening for patients detected by the hotline + early treatment of suspects (within 7 days)
  
  - 32 symptomatic screened and treated/17 continued treatment 10 days
  - 22 hospitalized/11 in ICU, 1 death

Personal communication from Prof. Pablo Bartolucci, DREPADO Network, H. Mondon Hospital, Paris; France
4. Data Collection

Objectives:

- To understand disease characteristics
- To optimize patient management in the acute setting and in long term follow up

Example in Europe:

ERN-EuroBloodNet Registry on patients with rare red blood cell defects and COVID-19 (Ethics approval 07/04/2020 PR(AG)215/2020 by University Hospital Vall d’Hebrón, Spain)

Longitudinal Data collection – excel sheet disseminated
A brief overview of the Thalassaemia International Federation (TIF) response to the COVID-19 Pandemic

Dr Androulla Eleftheriou

Executive Director, Thalassaemia International Federation

Cyprus
The global overview

Only about 5% of the global thalassaemia population live in countries able to provide optimal or near optimal care (based on International Guidelines) including patients living in countries with high standards of healthcare.

Even though thalassaemia syndromes do not in general have respiratory complications, as a standard clinical feature, sub-optimal control of the condition increases complications, may reduce immunity and increase possible risk factors for vulnerability to the SARS-CoV.
TIF’s response to the COVID-19 pandemic

Two-pillar approach:

1. Preparation of material with useful & valuable information for the patient community
   - COVID-19 Pandemic & Haemoglobin Disorders
   - Useful Health & Nutrition Short Guide for the COVID-19 Pandemic
   - TIF-Proposed Haemoglobinopathy Patient Pathway during the COVID-19 Pandemic
   - Q&A: The COVID-19 Pandemic & the Haemoglobinopathy Patient
   - Developing Vaccinations & Therapeutic Drugs for COVID-19: A Guide
   - Blood & COVID-19 Guide

2. Continuous collection of clinical & other information on SARS-COV-2 infections in patients with haemoglobin disorders & engagement with the patient community
TIF’s response to the COVID-19 pandemic: Engaging with the Patient Community

- Contribution to the work of a global thalassaemia & SCD survey
- **TIF Disease-specific survey** to 268 treating physicians, in 154 thalassaemia clinics/centres across 56 countries with the purpose of collecting clinical data about thalassaemia patients who have been infected with the SARS-CoV-2 virus on a global scale
- **TIF COVID-19 Helpdesk** for issues specifically related to the pandemic – TIF-COVID19@thalassaemia.org.cy
- **Q&A Webinar Series with patient leaders** from 48 countries
- **Peer-to-Peer support & guidance** through TIF communication channels (mainly TPC What’s Up group and Facebook)
- Distribution of educational globally more than 50,000 recipients’ across 62 countries including patient support groups (thalassaemia and sickle cell disease), haematologists, paediatricians, national health authorities, regional and international health bodies, professional societies, treating centres etc.
- **Video message** from TIF’s President, Executive Director and Medical Advisor
- Promotion of Blood Donation through the creation of **TIF Social Media Banners & Covers**
A TIF-Proposed Haemoglobinopathy Patient Pathway during the COVID-19 Pandemic

Transfusion – related

Notable Points:

☑️ 2 – step Triage (once on the telephone, once outside the Day centre)

☑️ Triage repeated on cross-match day and transfusion day

☑️ Hb level checked at Triage

☑️ Isolation room with a separate entrance / exit
A TIF-Proposed Haemoglobinopathy Patient Pathway during the COVID-19 Pandemic

NOT transfusion – related

Notable Points:

- **Virtual consultations** to be preferred wherever possible
- **2 – step Triage** (once on the telephone, once outside the Day centre)
- **Isolation room** with a separate entrance / exit

---

**Haemoglobinopathy Patient Pathway during COVID-19 Outbreak (Not Transfusion Related)**

START: Patient calls day centre to report feeling unwell (transfusion not due soon)

Discuss symptoms with doctor over the phone

Is it necessary for the patient to visit the day care centre for further examination?

- **yes!**
  - Provide advice over the telephone
  - Follow national guidelines for suspected COVID-19 incidents (see proposed testing algorithm)

- **no**
  - Permit admission to day care centre for further medical examination in “Isolation Room”

Does the patient have COVID-19 related symptoms?

- **yes!**
  - Refer patient to COVID-19 hospital unit & maintain communication with medical personnel for thalassaemia-related aspects of treatment (transfusions during the period of COVID-19 infection should take place at the COVID-19 hospital unit)

- **no**
  - Provide patient with relevant medical advice

On arrival at the day care centre, a separate TRIAGE area, outside the hospital / clinic / centre should be available (see role of triage below)

Do the tests confirm COVID-19?

- **yes!**
  - Permit admission to day care centre for further medical examination in “Isolation Room”

- **no**
  - Provide patient with relevant medical advice

Refer patient to COVID-19 hospital unit & maintain communication with medical personnel for thalassaemia-related aspects of treatment (transfusions during the period of COVID-19 infection should take place at the COVID-19 hospital unit)

It is advisable to follow the International Guidelines for the Clinical Management of Transfusion Dependent Thalassaemia (TDT), Non-Transfusion Dependent Thalassaemia (NTDT) and Emergency Care, compiled by international Experts in the field and published by TIF, wherever possible. Available at www.thalassaemia.org.cy
A TIF-Proposed Haemoglobinopathy Patient Pathway during the COVID-19 Pandemic

**IMPACT**

98% of TIF members in European countries report adoption or customisation of TIF’s proposed patient pathway

< 2% of TIF members outside Europe report such adjustments to their day clinics

62% of patients (98.5% in developing countries) are totally deprived of MDC (including important monitoring laboratory tests e.g. ferritin levels)

38% are observing postponements of MDC examinations (91.7% in the West, 3.6% in W. Pacific, 2.8% in M. East and 1.9% in private hospitals of SEA countries)

MDC = Multi-disciplinary care including (1) MRI Heart & Liver Iron and (2) Liver, Heart & Endocrine Monitoring

An ongoing flow of information is reaching TIF on a daily basis

Conclusion

There are many questions and many concerns!

Are thalassaemia patients protected due to (1) their regular blood transfusion therapy, and/or (2) the strict measures taken for the safety of vulnerable groups (like patients with haemoglobin disorders) in every country, and/or (3) a special mechanism(s) that may perhaps allow thalassaemia patients to have better survival and better outcomes in the course of this COVID-19 outbreak?

Very importantly however, there are many unknowns on the aspects of the virus, its infection in humans and its consequences.

Will adequate data on the impact of COVID-19 in thalassaemia be collected? Perhaps this discussion can be reconvened in 20 – 25 days.

Developing COVID-19 Vaccines at Pandemic Speed

Lurie, N et al, NEJM, April 15th 2020
Thank you for your participation!  
To be continued.

Visit the EHA COVID-19 web page: www.ehaweb.org/covid-19/  
for more webinars, to get access to the EHA COVID-19 hematology hub  
and for more COVID-19 hematology resources.

The content discussed during this webinar is based on the personal experiences & opinions of the speakers.  
No general, evidence-based guidance can be derived from this discussion.