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# Interim guidance for the appropriate support of people with enzymopenia G6PD (favism) in the current SARS-CoV-2 emergency scenario

ISS COVID-19 Rare Diseases Working Group

Version April 14, 2020

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## ISS COVID-19 Rare Diseases Working Group

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This report provides interim indications for appropriate support to people with deficiency of G6PD enzyme (favism) in the current SARS-CoV-2 emergency scenario. The G6PD deficiency is an endemic condition in our Country and people with this deficit are almost always asymptomatic, however some factors inducing oxidative stress on red blood cells can trigger hemolytic crises. The onset and intensity of the hemolytic crisis depends on the dose of the triggering agent. These agents include drugs such as chloroquine and hydroxychloroquine, authorized by AIFA (Italian Medicines Agency) and used in patients to deal with the SARS-CoV-2 coronavirus pandemic in the absence of proven effective treatment. In order to ensure correct management of the SARS-CoV-2 patient, it is necessary to characterize his G6PD status before starting the pharmacological treatment with chloroquine or hydroxychloroquine, through the medical history or by the screening or quantitative test of G6PD activity. Therefore, it is necessary to give adequate attention to the warning on the use of chloroquine and hydroxychloroquine in the presence of the enzyme G6PD deficiency.

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# Introduction

G6PD (glucose-6-phosphate dehydrogenase) is an enzyme expressed ubiquitously in all cells (housekeeping gene). However, its deficiency has potential pathological consequences almost exclusively in red blood cells (1,2).

G6PD deficiency is by far the most frequent erythrocyte enzymopathy in the human species. It has been estimated that at least 500 million people have a mutant gene which leads to a defect in the activity of the G6PD. Globally the G6PD deficiency is widely distributed and is particularly frequent in Africa, the Middle East, Asia and the Mediterranean area.

The enzymatic variants of G6PD have diverse levels of enzyme activity and this leads to different clinical manifestations (3,4):

- the Class I variants, very rare, have severe enzyme deficiency (10-20% of normal activity) and bring to chronic hemolytic anemia;
- the Class II variants, such as the Mediterranean G6PD, very frequent in Italy, have even more severe enzyme deficit (<10% of normal activity) with risk of acute hemolytic anemia episodes;
- the Class III variants, such as the G6PD Seattle, very frequent in Italy, and the G6PD A-, observed in populations of African origin, have from severe to moderate enzyme deficit (10-60% of normal activity) and show rare cases of acute hemolytic anemia.

In Italy, the enzymopenia G6PD is often incorrectly called favism, since the hemolytic crisis due to the ingestion of fava beans is the best-known clinical manifestation.

**People with G6PD deficiency are mostly asymptomatic and hemolysis is determined** – with very few exceptions – **by a triggering factor** (3,4).

The factors triggering the hemolytic crisis are:

- Ingestion of fava beans
- Intake of drugs with intracellular oxidizing action
- Exposure to substances with intracellular oxidizing action
- Bacterial and viral infections (medium to severe)

The listed trigger factors, although apparently heterogeneous, have in common the oxidative action on red blood cells.

Since the onset and intensity of the hemolytic crisis depend on the dose of the triggering agent, the crisis does not necessarily occur after an exposure to one of the listed factors.

Moreover, as crises can arise at every stage of life and even in old age in a deficient G6PD subject, the absence of previous hemolytic crises does NOT reduce the risk, as a crisis can arise at any time.

# Clinical framework

The majority of subjects with G6PD enzymopenia are asymptomatic for life: in other words, the deficit of G6PD allows a perfectly normal life in terms of life expectancy and quality of life. Individuals may not know that they are carriers of G6PD deficiency, in absence of evident clinical signs.

Spontaneous clinical manifestations occur only in the neonatal period; afterwards, acute hemolytic crises can be triggered by the ingestion of fava beans, by infections, or by the intake of certain drugs (3,4).

## Severe and / or prolonged neonatal jaundice

The neonatal period is critical as G6PD deficiency can cause persistent jaundice in the newborn, a condition that if untreated can cause significant damage and mental retardation.

## Acute hemolytic anemia

The acute hemolytic crisis can be caused by the ingestion of fava beans (hence favism), by the intake of some types of drugs (3-6), by infectious episodes, both bacterial and viral, and by diabetic ketoacidosis. Particularly severe and rapid acute hemolytic crises can cause acute renal failure (very rare in children).

## Chronic non-spherocytic hemolytic

This condition (known as CNSHA) is a rare form of G6PD enzymopenia (almost exclusively in males) due to a G6PD variant of Class I.

# Clinical manifestations

Wherever fava beans are a common food, the most frequent manifestation of G6PD deficiency is the hemolytic crisis triggered by the ingestion of fava beans, called favism. The inhalation of pollen from flowering fava beans does not cause favism, therefore the prohibition on cultivating fava beans near inhabited centers or near the home of deficient G6PD subjects is not based on any scientific evidence (3, 7).

As already mentioned, the hemolytic crisis from fava beans ingestion or from drugs is strongly dose-dependent, therefore, it does not necessarily occur after ingestion. On the other hand, the absence of previous hemolytic crises does not lead to a reduction of risk, as hemolytic crises can appear at any age (3).

Hemolytic crises occur after a few days (from 2 to 7 days) from exposure to the triggering agent and the severity of the clinical manifestations is very variable, depending both on individual characteristics (type of G6PD variant, presence of other diseases, triggering factors such as infections) and on drug characteristics (oxidizing power, dose, duration of exposure). In the case of class III variants, such as A-, drug-induced hemolysis is generally self-limiting, while in presence of class II enzyme variants, such as Mediterranean G6PD, hemolysis continues without compensatory effect (4).

Hemizygous male subjects and female homozygous for G6PD class II variants exhibit extremely low activity values, and are highly susceptible to oxidizing drugs, and other factors. Heterozygous females, on the other hand, may have G6PD activities ranging from very low values, comparable to those of hemizygous male subjects, up to normal values. Therefore, a hemolytic crisis may occur in these subjects in relation to the deficit of G6PD activity (4).

# Diagnostics

The diagnosis of G6PD deficiency is performed through qualitative tests (screening tests) and quantitative tests and is carried out on blood samples withdrawn with anticoagulant (8).

Screening tests (such as the fluorescence spot test that requires only one drop of blood placed on filter paper) are generally used to identify individuals with G6PD deficiency in neonatal screening programs or to screen populations where the incidence of the enzymatic defect is high (for example in Sardinia). The positivity to the screening test has to be confirmed by a quantitative test that measures the G6PD activity.

The quantitative test for G6PD allows to identify an eventual G6PD deficiency and to determine its severity.

The test allows to diagnose the deficit in hemizygous males, and in homozygous females with a double mutation, which have G6PD activity values lower than 30% of normal. In heterozygous females, activity levels are intermediate and highly variable, and, in some cases, diagnosis is not possible without a family study and genetic analysis.

In summary, male subject with normal levels of G6PD activity, have no G6PD deficiency, while females with normal levels of G6PD activity might be heterozygous carriers.

The measurement of G6PD activity is mainly performed on patients who have experienced symptoms of anemia (such as fatigue, pallor, a rapid heart rate) and / or jaundice. The analysis carried out while the symptoms manifest should be repeated also subsequently, to confirm the activity levels of the G6PD.

The measure of G6PD activity can be prescribed for children who have persistent jaundice and to whom another cause has not been identified. It can also be requested for patients of all ages who have had one or more episodes of hemolytic anemia, especially coinciding with viral or bacterial infections or who have been exposed to agents that can trigger the hemolytic crisis (such as fava beans, mothballs, drugs) in the previous 24-48 hours.

# SARS-CoV-2 infection and G6PD enzymopenia

The respiratory disease caused by the new coronavirus has been called COVID-19 by the World Health Organization (WHO) and is due to the infection of a new strain of coronavirus to which the International Committee on Taxonomy of Viruses (ICTV) has assigned the definitive name ***Syndrome Acute Respiratory Severe Coronavirus 2*** (SARS-CoV-2).

The most common symptoms of a coronavirus infection in humans include fever, cough and breathing difficulties. Some patients may experience soreness and muscle pain, nasal congestion, sore throat, anosmia and diarrhea. These symptoms are generally mild and begin gradually. In severe cases, the infection can cause pneumonia, severe acute respiratory syndrome, kidney failure and even death.

Older people and those with pre-existing diseases, such as hypertension, heart disease or diabetes, and immunosuppressed patients (for congenital or acquired pathology or being treated with immunosuppressant, transplanted patients) are more likely to develop severe forms of the disease.

According to currently available data, symptomatic people are the most frequent cause of the virus spreading. The WHO considers new coronavirus infection infrequent before symptoms develop.

The incubation period varies between 2 and 12 days; 14 days represent the maximum precautionary limit.

To date there are no data indicating that there is a particular susceptibility of subjects with G6PD deficiency to SARS-CoV-2 infection.

There are currently no specific drugs for the treatment of this disease, and patients with SARS-CoV-2 infection are treated with several existing drugs that are already used for other viral infections.

The Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA), together with its Technical Scientific Commission, is constantly engaged in the management of the COVID-19 emergency, in relation to the use of drugs for the treatment of patients in this pandemic. Some of these medicines are available exclusively within clinical trials while others, which are accessible on the market with other therapeutic indications, have been provided by the National Health Service (NHS) with specific measures.

# G6PD enzymopenia and drugs for SARS-CoV-2

The AIFA has authorized the off-label use of some drugs, paid by the NHS, in derogation of Law 648/1996 such as the lopinavir / ritonavir association (and in the alternative darunavir in combination with cobicistat or ritonavir) and chloroquine or hydroxychloroquine, to deal with the pandemic coronavirus SARS-CoV-2 in the absence of proven treatment (9).

Chloroquine, a drug used for the prevention and treatment of malaria, has been shown both *in vitro* and *in vivo* to have antiviral activity against SARS and avian influenza, and thus it has been recommended at a dose of 500 mg 2 times a day (*Bis In Die*, BID) for 10 days in patients with SARS-CoV-2-associated pneumonia. Alternatively, the use of hydroxychloroquine (today authorized in the treatment of rheumatoid arthritis and lupus erythematosus) is recommended at a dose of 400 mg BID (1$^{st}$ day) and from the 2$^{nd}$ day 200 BID for 5-7 days according to the evolution of the disease (10, 11). The aforementioned indications have been implemented as part of the procedures for the acquisition of drugs for off-label use by IRCCS Lazzaro Spallanzani, including informed consent for the patient (12).

Both chloroquine and hydroxychloroquine can have serious side effects, even in subjects without G6PD deficiency (13), especially at high doses or in combination with other drugs (3). They must not be used without prescription and without medical supervision, and the prescription in case of COVID-19 must refer only to the case of clinical trials or protocols agreed at national level (EMA/170590/2020)

A potential widespread of the use of these drugs to all symptomatic patients, at a time when healthcare facilities are profoundly reorganizing themselves, requires the integration of knowledge and skills in the biomedical field in order to optimize the management of patients (14).

It is therefore of extreme importance to recall to all the healthcare professionals to extend to all patients the warning relating to the use of chloroquine and hydroxychloroquine, in case of presence of impaired activity of the glucose-6-phosphate dehydrogenase (G6PD).

People with G6PD deficiency have greater difficulties in metabolizing oxygen free radicals (ROS), developing in some cases severe forms of hemolytic anemia. Hemolysis is determined-with very rare exceptions-by a triggering factor such as the ingestion of fava beans and the intake of some drugs with intracellular oxidizing action. Chloroquine and hydroxychloroquine are among these drugs, having an oxidizing action. However, under normal conditions and in monotherapy, they do not give hemolysis, while other factors, such as the patient's immune status, bacterial or viral infections, the dose of the oxidizing drug and / or drugs interaction may contribute to determine this effect (1-4, 6, 15).

Therefore, for subjects with G6PD deficiency, SARS-CoV-2 infection represents an additional risk factor. Chloroquine and hydroxychloroquine currently applied to COVID-19 patients should be avoided in those with severe G6PD deficiency as they could trigger a hemolytic crisis in the patient.

Consequently, considering that the G6PD deficiency is an endemic condition in our country, and in order to guarantee the correct care of SARS-Cov2 positive patients it is necessary to assure the condition of the G6PD status before starting the pharmacological treatment with chloroquine or hydroxychloroquine, through a medical history and, if this is not possible and depending on the situation, through the screening or quantitative test of the G6PD activity. It is necessary to keep in mind that the absence of previous hemolytic crises in a person with G6PD deficiency does not lead to a reduction in risk, even in old age.

Yet, if the treatment with chloroquine or hydroxychloroquine has already been started without the possibility to obtain timely a dosage of the enzyme and in presence of both a drastic drop in hemoglobin

values, of at least 1.5-2 g/L at 3-5 days from start of treatment, and of dark urine, it is necessary to consider the presence of a deficiency of G6PD and to discontinue the treatment.

For the foregoing reasons and before the prescription, the healthcare professional has also to refer to the safety information note introduced by the AIFA for the appropriate use of chloroquine and hydroxychloroquine in patients with COVID-19, with particular reference to a precaution of use in the patient with G6PD deficiency (AIFA communication of 31.03.2020) (16).

In relation to all the medicines that can be used to treat COVID19 disease (whether they are made available for off-label use by the NHS or can only be used in clinical trials), the Scientific Technical Commission (CTS) of AIFA published the drug sheets, containing explicit therapeutic guidelines for a controlled and safe use in the context of the ongoing emergency, providing thus clinicians with useful elements to guide prescription and to define, for each used drug, a relationship between benefits and risks for the individual patient (9).

Below the links to the aforementioned drug sheets, updated on 08.04.2020:

- **Azithromycin**
  https://www.aifa.gov.it/documents/20142/1123276/azitromicina_08.04.2020.pdf/951fa605-0bf9-3882-ae2f-15128fe97a1b.

- **Lopinavir/ritonavir**
  https://www.aifa.gov.it/documents/20142/0/lopinavir_ritonavir_02.04.2020.pdf/64b8cf03-acf1-e9fa-80fa-c6d3ecba5f7d

- **Darunavir/cobicistat**
  https://www.aifa.gov.it/documents/20142/0/darunavir_cobicistat_01.04.2020.pdf/34c4938d-5b25-e39c-abb3-b42e3c874e1b

- **Hydroxychloroquine**
  https://www.aifa.gov.it/documents/20142/0/idrossiclorochina_02.04.2020.pdf/9b4cf710-44ec-3a8e-8493-649d96cfb106

# Recommendations

**A)** The deficiency of glucose-6-phosphate dehydrogenase (G6PD) is widespread in our country, therefore, in order to ensure the correct management of the positive SARS-CoV-2 patients it is necessary to check the condition of the G6PD status before starting the drug treatment with chloroquine or hydroxychloroquine:

1. accurately collect information on the history of the presence of the G6PD deficiency;
2. do a screen test (recommended only for male patients) or a quantitative test for G6PD activity.

**B)** The absence of previous hemolytic crisis in a person with G6PD deficiency does not lead to a reduction in risk, even in old age.

**C)** In patients with severe G6PD deficiency and with SARS-CoV-2 infection, pharmacological treatments with chloroquine or hydroxychloroquine should be avoided as they could trigger a severe hemolytic crisis.

**D)** It is necessary to recall to all healthcare professionals to extend to all patients the warning relating to the use of chloroquine and hydroxychloroquine, in the presence of impaired activity of the enzyme G6PD.

# References


1. Luzzatto L, Arese P. Favism and Glucose-6-Phosphate Dehydrogenase Deficiency. *N Engl J Med* 2018;378:60-71.

2. Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. *Lancet* 2008;371:64–74.

3. Barella S., De Franceschi L, Graziadei G, Iolascon A, Rigano P, Sorrentino F, Forni GL. *Enzimopenia G6PD* Roma: Società Italiana Talassemie ed Emoglobinopatie (SITE); 2018. Disponibile all'indirizzo: http://site-italia.org/file/collana_scientifica/g6pd/download.php?file=G6PD.pdf.

4. Maffi D, Caforio MP, Pasquino MT, Caprari P. *Deficit di glucosio-6-fosfato deidrogenasi e farmaci*. Roma: Istituto Superiore di Sanità; 2009. (Rapporti ISTISAN 09/47).

5. Elenco dei principi attivi da evitare in caso di carenza di Glucosio-6-Fosfato Deidrogenasi (G6PD), elaborato dall'Agenzia Italiana del Farmaco (AIFA) sulla base di quanto predisposto dall'Agenzia dei Farmaci Francese (aggiornato al febbraio 2008) e del Rapporto ISTISAN 99/19 dell'Istituto Superiore di Sanità. Disponibile all'indirizzo: http://www.agenziafarmaco.gov.it/sites/default/files/elenco_dei_farmaci_G6PD.pdf.

6. ANSM. *Medicaments et deficit en glucose-6-phosphate deshydrogenase (G6PD): Classement des medicaments par substance active.* Agence nationale de sécurité du médicament et des produits de santé; 2014.

7. Ministero della Salute, Dipartimento della Sanità pubblica veterinaria, della sicurezza alimentare e degli organi collegiali per la tutela della salute, Comitato Nazionale per la Sicurezza Alimentare. *Parere N. 9 del 19/11/2012 Problematiche relative al favismo* http://www.salute.gov.it/imgs/C_17_pubblicazioni_1906_allegato.pdf

8. Roper D, Layton M, Rees D, Lambert C, Vulliamy T, De la Salle B, D'Souza C. British Society of Haematology. Laboratory diagnosis of G6PD deficiency. A British Society for Haematology Guideline. *Br J Haematol* 2020 (28 January 2020) https://doi.org/10.1111/bjh.16366.

9. AIFA. *Azioni intraprese per favorire la ricerca e l'accesso ai nuovi farmaci per il trattamento del COVID-19.* Disponibile all'indirizzo: https://www.aifa.gov.it/fr/-/azioni-intraprese-per-favorire-la-ricerca-e-l-accesso-ai-nuovi-farmaci-per-il-trattamento-del-covid-19.

10. Multicenter collaboration group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia. [Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia]. *ZhonghuaJie He HeHuXi Za Zhi*. 2020 Feb 20;43(0): E019.

11. AIFA Idrossiclorochina nella terapia dei pazienti adulti con COVID-19. Disponibile all'indirizzo: https://www.aifa.gov.it/documents/20142/0/idrossiclorochina_02.04.2020.pdf/9b4cf710-44ec-3a8e-8493-649d96cfb106.

12. Indicazioni per le procedure relative all'acquisizione dei farmaci per uso *off-labell* opinavir/ritonavir e clorochina, e per uso compassionevole di remdesivir. Roma: IRCCS Lazzaro Spallanzani. Disponibile all'indirizzo: https://www.inmi.it/wp-content/uploads/2020/04/4-COVID-19-Allegato-1-13-marzo-2020.pdf.

13. Mohammad S, Clowse MEB, Eudy AM, Criscione-Schreiber LG. Examination of hydroxychloroquine use and hemolytic anemia in G6PDH-deficient patients. *Arthritis Care & Research* 2018; 70:481.

14. De Franceschi L, Costa E, Dima F, Morandi M, Olivieri O. Acute hemolysis by hydroxycloroquine was observed in G6PD deficient patient with severe COVD-19 related lung injury. *Eur J Intern Med* (in press).

15. Expert Opinion Società Italiana Talassemie ed Emoglobinopatie SITE (sito http://site-italia.org/2020/covid-19_idrossiclorochina-g6pd.php.

16. Comunicazione AIFA sull'utilizzo di Clorochina e Idrossiclorochina nella terapia dei pazienti affetti da COVID-19 - Informazioni di sicurezza. Disponibile all'indirizzo: https://www.aifa.gov.it/-/comunicazione-aifa-sull-utilizzo-di-clorochina-e-idrossiclorochina-nella-terapia-dei-pazienti-affetti-da-covid-19-informazioni-di-sicurezza.

# Rapporti ISS COVID-19 in Italian

**Available from** https://www.iss.it/rapporti-covid-19

1. Gruppo di lavoro ISS Prevenzione e controllo delle Infezioni.
   *Indicazioni ad interim per l'effettuazione dell'isolamento e della assistenza sanitaria domiciliare nell'attuale contesto COVID-19.* Versione del 7 marzo 2020.
   Roma: Istituto Superiore di Sanità; 2020 (Rapporto ISS COVID-19, n. 1/2020)

2. Gruppo di lavoro ISS Prevenzione e controllo delle Infezioni.
   *Indicazioni* ad interim *per un utilizzo razionale delle protezioni per infezione da SARS-CoV-2 nelle attività sanitarie e sociosanitarie (assistenza a soggetti affetti da COVID-19) nell'attuale scenario emergenziale SARS-CoV-2.* Versione del 28 marzo 2020.
   Roma: Istituto Superiore di Sanità; 2020 (Rapporto ISS COVID-19, n. 2 Rev./2020)

3. Gruppo di lavoro ISS Ambiente e Gestione dei Rifiuti.
   *Indicazioni* ad interim *per la gestione dei rifiuti urbani in relazione alla trasmissione dell'infezione da virus SARS-CoV-2.* Versione del 31 marzo 2020.
   Roma: Istituto Superiore di Sanità; 2020 (Rapporto ISS COVID-19, n. 3 Rev./2020)

4. Gruppo di lavoro ISS Prevenzione e controllo delle Infezioni.
   *Indicazioni ad interim per la prevenzione e il controllo dell'infezione da SARS-CoV-2 in strutture residenziali sociosanitarie.* Versione del 16 marzo 2020.
   Roma: Istituto Superiore di Sanità; 2020 (Rapporto ISS COVID-19, n. 4/2020)

5. Gruppo di lavoro ISS Ambiente e Qualità dell'aria *indoor*.
   *Indicazioni ad per la prevenzione e gestione degli ambienti indoor in relazione alla trasmissione dell'infezione da virus SARS-CoV-2.* Versione del 23 marzo 2020.
   Roma: Istituto Superiore di Sanità; 2020. (Rapporto ISS COVID-19, n. 5/2020).

6. Gruppo di lavoro ISS Cause di morte COVID-19.
   *Procedura per l'esecuzione di riscontri diagnostici in pazienti deceduti con infezione da SARS-CoV-2.* Versione del 23 marzo 2020.
   Roma: Istituto Superiore di Sanità; 2020. (Rapporto ISS COVID-19, n. 6/2020).

7. Gruppo di lavoro ISS Biocidi COVID-19 e Gruppo di lavoro ISS Ambiente e Rifiuti COVID-19.
   *Raccomandazioni per la disinfezione di ambienti esterni e superfici stradali per la prevenzione della trasmissione dell'infezione da SARS-CoV-2.* Versione del 29 marzo 2020.
   Roma: Istituto Superiore di Sanità; 2020. (Rapporto ISS COVID-19, n. 7/2020).

8. Osservatorio Nazionale Autismo ISS.
   *Indicazioni ad interim per un appropriato sostegno delle persone nello spettro autistico nell'attuale scenario emergenziale SARS-CoV-2.* Versione del 30 marzo 2020.
   Roma: Istituto Superiore di Sanità; 2020. (Rapporto ISS COVID-19, n. 8/2020).

9. Gruppo di Lavoro ISS Ambiente – Rifiuti COVID-19.
   *Indicazioni ad interim sulla gestione dei fanghi di depurazione per la prevenzione della diffusione del virus SARS-CoV-2. Versione del 3 aprile 2020.*
   Roma: Istituto Superiore di Sanità; 2020. (Rapporto ISS COVID-19, n. 9/2020).

10. Gruppo di Lavoro ISS Ambiente-Rifiuti COVID-19.
*Indicazioni ad interim su acqua e servizi igienici in relazione alla diffusione del virus SARS-CoV-2 Versione del 7 aprile 2020.*
Roma: Istituto Superiore di Sanità; 2020. (Rapporto ISS COVID-19, n. 10/2020).

11. Gruppo di Lavoro ISS Diagnostica e sorveglianza microbiologica COVID-19: aspetti di analisi molecolare e sierologica
*Raccomandazioni per il corretto prelievo, conservazione e analisi sul tampone oro/nasofaringeo per la diagnosi di COVID-19. Versione del 7 aprile 2020.*
Roma: Istituto Superiore di Sanità; 2020. (Rapporto ISS COVID-19, n. 11/2020).

12. Gabbrielli F, Bertinato L, De Filippis G, Bonomini M, Cipolla M.
*Indicazioni ad interim per servizi assistenziali di telemedicina durante l'emergenza sanitaria COVID-19. Versione del 13 aprile 2020.*
Roma: Istituto Superiore di Sanità; 2020. (Rapporto ISS COVID-19, n. 12/2020).

13. Gruppo di lavoro ISS Ricerca traslazionale COVID-19.
*Raccomandazioni per raccolta, trasporto e conservazione di campioni biologici COVID-19. Versione del 15 aprile 2020.*
Roma: Istituto Superiore di Sanità; 2020. (Rapporto ISS COVID-19, n. 13/2020).

14. Gruppo di lavoro ISS Malattie Rare COVID-19.
*Indicazioni ad interim per un appropriato sostegno delle persone con enzimopenia G6PD (favismo) nell'attuale scenario emergenziale SARS-CoV-2. Versione del 14 aprile 2020.*
Roma: Istituto Superiore di Sanità; 2020. (Rapporto ISS COVID-19, n. 14/2020).