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Interim guidance for the appropriate support of adrenal insufficiency in children during the current SARS-CoV-2 pandemic emergency

ISS COVID-19 Rare Diseases Working Group

Version of May 10, 2020

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This report provides ad interim guidance for the appropriate support of children and adolescents with adrenal insufficiency during the current SARS-CoV-2 pandemic emergency. Adrenal insufficiency is a potentially lethal disease, characterized by a deficit in the production or action of glucocorticoids, sometimes associated with insufficiency of mineralcorticoids and androgens. The main clinical symptoms of adrenal insufficiency include weakness, fatigue, anorexia, nausea and vomiting, abdominal pain, weight loss, postural hypotension and in some cases desire to eat salt. In general, the diagnosis and treatment of patients with adrenal insufficiency is very demanding. In particular, the presence of fever ≥ 38°C, acute infection, stress such as surgery and other acute conditions can alter the metabolic status to such an extent that, if not treated properly, adrenal crisis in many forms of adrenal insufficiency may occur. Adrenal crisis is a critical emergency requiring immediate action, appropriate treatment and hospitalization, because it is potentially lethal. In case of suspected or confirmed COVID-19, cortisone replacement therapy must be continued and, depending on clinical severity, increased appropriately to guarantee adequate hormonal and cardiovascular support during conditions of physiological stress. Contact with reference centres to ensure advice from specialists is highly recommended, also through the use of telemedicine systems.

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SARS-CoV-2 infection in children

Compared to the level of knowledge on the adult population, the prevalence of SARS-CoV-2 infection in the paediatric population is unknown. Current available scientific evidence indicates that in children, COVID-19 is a much less dramatic illness with significantly lower mortality than in adults.

A first review of the data of children with COVID-19 was performed in China and concludes that of 2143 children with confirmed infection, only 112 (5.6%) developed a severe form of the disease (defined as the presence of hypoxia / dyspnoea) and 13 (0.6%) developed Acute Respiratory Distress Syndrome (ARDS) (1).

A review of the literature made in April 2020 confirmed these statistics, even though the accentuation of the bronchial texture and "frosted glass" opacity on radiological examination were noted even in asymptomatic children (2).

In April 2020, the CDC (Centers for Disease Control and prevention in USA) published a second study. Out of 149,760 cases of SARS-CoV-2 with positive nasopharyngeal swab PCR tests who were identified between 12 February and 2 April, only 2,500 were children/adolescents under the age of 18. The presence of clinical symptoms suggestive of COVID-19 (fever, cough and dyspnoea) was observed in 73% of the 2500 paediatric SARS-CoV-2 positives whereas 93% of the positive adults were symptomatic. The same document highlights a hospitalization rate of at least 5.7%, and an ICU hospitalization ranging between 0.58% and 2%. In the paediatric group, 62% of hospitalized children were aged 12 months or less and five of 15 infants needed intensive care. About 77% of hospitalized patients, including all ICU patients, had one or more concomitant condition, whereas only 12% of non-hospitalized children had concomitant conditions (3).

In a series of 41 Spanish paediatric patients with confirmed SARS-CoV-2 infection, 25 required hospitalization, 4 patients required intensive care and another 4 patients needed respiratory assistance via nasal cannulas (4).

In Italy, ISS data report that up until May 7, 2020, of the 25,452 deaths with positivity for SARS-CoV-2 infection, only three cases were in the 0-19 years age group (5).

In a series of 100 children with SARS-CoV-2 positive swabs who entered the emergency room of 17 Italian hospitals, only 52% of patients with fever had the other two symptoms suggestive of COVID-19 (cough and dyspnoea). Thirty-eight of the children required hospitalization, 9 of whom needed respiratory support (6 with pre-existing diseases). All 100 children in the series have recovered (6).

These data indicate an overall infection and mortality rate in children that is significantly below the 4% rate reported in adults with COVID-19, thus reducing the concerns of doctors and parents. However, more attention should be paid to children with less than one year of age and to those with concomitant conditions who show the symptoms of the infection.

Studies performed on pregnant mothers infected with SARS-CoV-2 exploring the relationship between maternal immunity and protection of the infant from infection, did not reach conclusive results (7). "Suspicious" symptoms such as fever, no response to therapy, difficulty breathing, cough and sleepiness in infants born form a SARS-CoV-2 positive mother should alert the parents and the paediatrician.

Patients with hypoadrenalism are more at risk of contracting infections (8-10) and, in case of suspected or confirmed COVID-19, cortisone replacement therapy must be continued, or, depending on clinical severity, increased appropriately to guarantee adequate hormonal and cardiovascular support during

conditions of physiological stress. Contact with reference centres to ensure advices from specialists is highly recommended, also through the use of telemedicine systems.

Adrenal insufficiency and SARS-CoV-2

Introduction

Adrenal Insufficiency (or hyposurrenalism) is a potentially lethal disease, characterized by a deficit in the production or action of glucocorticoids, with or without deficiency in mineralcorticoids and adrenal androgens.

It can result from primary adrenal failure or secondary adrenal disease due to impairment of the hypothalamic-pituitary axis (central adrenal insufficiency). In the context of central adrenal insufficiency, we distinguish a secondary form caused by an insufficient pituitary ACTH production and a tertiary form due to an altered hypothalamic function with inadequate secretion of CRF (11).

The estimated incidence of the primary form is 4.4-6 new cases per million inhabitants per year. Tuberculosis was the most common cause of primary adrenal insufficiency in the first half of the 20th century, but today the most frequent form is that of autoimmune disease. The frequency of the various forms of primary insufficiency in children differs substantially from that of the adult population, with genetic forms being the most common in children, in particular the classic form of congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Secondary adrenal insufficiency is more common than the primary form. It has an estimated prevalence of 150-280 affected per million/year and affects women more frequently than men.

The most common cause of tertiary adrenal insufficiency is the long-term administration of exogenous glucocorticoids, which leads to prolonged suppression of the hypothalamic secretion of the hormone that releases corticotropin.

The main clinical symptoms of adrenal insufficiency include weakness, fatigue, anorexia, nausea and vomiting, abdominal pain, weight loss, postural hypotension and salt craving, while clinical features of a life-threatening adrenal crisis include vomiting, abdominal pain, myalgia, aching joints, severe hypotension and hypovolemic shock.

Before 1949, adrenal insufficiency was a fatal disease. The current availability of cortisone therapy has changed its prognosis. Today, particularly for paediatric patients, extremely effective synthetic products – hydrocortisone and fludrocortisone – are available for the treatment of glucocorticoid and mineralcorticoid deficiencies respectively.

Despite these great therapeutic breakthroughs, the diagnosis and treatment of patients with the disease remains challenging. In particular, fever (≥ 38°C), infections, stress, trauma and other acute conditions can drastically alter the metabolic status.

In the event of the onset of “adrenal crisis”, patient management becomes more complex and the prognosis can be poor if the patient is not treated promptly and adequately with increased doses of hydrocortisone, intravenous infusion of physiological saline and glucose.

Main causes of adrenal insufficiency

Tables 1-3 report the main causes of primary, secondary and tertiary adrenal insufficiency (11).

Table 1. Causes of primary adrenal insufficiency

Diseases	Clinical manifestations in addition to adrenal insufficiency
Non genetic disorders	
Autoimmune adrenalitis	
Isolated	Chronic mucocutaneous candidiasis, hypoparathyroidism and other autoimmune diseases (type 1); Thyroid autoimmune disease, type 1 diabetes and other autoimmune diseases (type2); Other autoimmune diseases excluding thyroid disease and type 1 diabetes (type 4)
Syndromic: APS type 1(APECED), type 2 and type 4	
Infectious adrenalitis	
Tuberculous adrenalitis	Symptoms and signs of underlying disease
AIDS	
Fungal adrenalitis	
Infiltrative forms	
Tumours	Symptoms and signs of underlying disease
Non tumors (amyloidosis, haemochromatosis)	
Bilateral adrenal haemorrhage	Meningococcal sepsis, perinatal events
Iatrogenic forms	
Bilateral adrenalectomy	Unresolved Cushing's syndrome, bilateral adrenal masses, phaeochromocytoma
Drug-induced adrenal insufficiency (anticoagulants, phenobarbital, ketoconazole, rifampicin, etc.)	None, unless related to drug
Genetic disorders	
Adrenoleukodystrophy	Weakness, spasticity, dementia, blindness, quadriparesis.
Congenital adrenal hyperplasia	
21-hydroxylase deficiency	Hyperandrogenism
11β-hydroxylase deficiency	Hyperandrogenism, hypertension
Others rarer enzyme deficiencies	
Smith-Lemli-Opitz syndrome	Craniofacial malformations, mental retardation, growth failure, hyponatraemia, hyperkalaemia, cholesterol deficiency
Adrenal hypoplasia congenital	
X-linked	Hypogonadotropic hypogonadism in boys
Xp21 contiguous gene syndrome	Duchenne muscular dystrophy, glycerol kinase deficiency, psychomotor retardation
SF-1-linked	XY sex reversal
Familial glucocorticoid deficiency or corticotropin insensitivity syndromes (type 1, type 2 and variants)	Hyperpigmentation, characteristic facial features, lethargy, muscle, weakness and altered growth rate
Triple A syndrome (Allgrove's syndrome)	Achalasia, alacrima, deafness, mental retardation, hyperkeratosis
Other rare syndromes (IMAGe syndrome, Kearns-Sayre syndrome, Wolman's disease, Sitosterolaemia)	Symptoms and signs of underlying disease

Table 2. Causes of secondary adrenal insufficiency

Diseases	Clinical manifestations in addition to adrenal insufficiency
Space-occupying lesions or trauma	
Pituitary tumors (adenomas, cysts, craniopharyngiomas, ependymomas, meningiomas, rarely carcinomas) or trauma (pituitary stalk lesions)	Panhypopituitarism
Pituitary surgery or irradiation for pituitary tumors, tumors outside the HPA axis or leukemia	Panhypopituitarism
Infections or infiltrative processes	Panhypopituitarism
Pituitary apoplexy	Abrupt onset of severe headache, visual disturbance, nausea, vomiting; panhypopituitarism
Genetic disorders	
Transcription factors involved in pituitary development disorders	Panhypopituitarism and other symptoms related to the specific transcription factor involved
Congenital pro-opiomelanocortin deficiency	Early-onset severe obesity, hyperphagia, red hair
Prader Willi Syndrome	Hypotonia, obesity, mental retardation, hypogonadism

Table 3. Causes of tertiary adrenal insufficiency

Diseases	Clinical manifestations in addition to adrenal insufficiency
Space-occupying lesions or trauma	
Hypothalamic tumours (craniopharyngiomas)	Panhypopituitarism
Hypothalamic surgery or irradiation for CNS or nasopharyngeal tumours	Panhypopituitarism
Infections or infiltrative processes	Panhypopituitarism
Trauma, injury	Panhypopituitarism
Drug-induced adrenal insufficiency	
Glucocorticoid therapy (systemic or topical) or endogenous glucocorticoid hypersecretion (Cushing's syndrome)	Symptoms and signs of underlying disease
Mifepristone	If excessive it can cause severe glucocorticoid deficiency
Antipsychotics(chlorpromazine), antidepressants (imipramine)	None, unless related to drug

Operational guidance

a. Procedures for delivery of therapies

The treatment is provided following the issue of a therapeutic plan by an accredited regional reference centre. As a result of the emergency for the COVID-19 pandemic, AIFA (Agenzia Italiana del Farmaco, the Italian Medicines Agency) has extended the validity to 90 days after expiry of web-based or paper-based treatment plans (PT), signed by specialist doctors (including rare diseases) in March and April (12).

b. Procedures for carrying out clinical tests

Normal practices in use should be adopted. Blood chemistry tests can be performed in any certified analytic laboratory on the advice of the attending physician or of the centre identified by the regions.

c. Management of therapy during infection

In the event of suspected or established COVID-19, patients on replacement therapy must continue the treatment. The dosage of hydrocortisone, which usually varies from 10 to 15 mg/m^2 of body surface area divided into 2-3 administrations / day depending on the type of adrenal insufficiency, has to be modified as indicated in all cases of acute intercurrent illness, doubling or tripling the dosage, depending on the presence of fever, its duration and on the patient's clinical condition (11-15). If oral intake is impossible (e.g., vomiting), hydrocortisone should be administered parenterally (IM or IV). However, constant contact with the reference canter is recommended to allow an assessment by the specialist to prevent adrenal crisis. If a crisis still occurs, urgent hospitalization is necessary. Parents of children with adrenal insufficiency are recommended, as generally suggested by specialists, to make sure they have sufficient quantities of medications, including the intramuscular liquid formulation (IM), even if at present there are no reports of hydrocortisone and fludrocortisone deficiencies.

d. Assessment of infectious risk

Currently there is no epidemiological evidence that both paediatric and adult patients with adrenal insufficiency are at an increased risk of contracting SARS-CoV-2 infection or that the clinical course of the illness would be different from that of the general population. However, patients with adrenal insufficiency must be considered at/as “high risk” in the context of the prevention and management of SARS-CoV-2 infection. They may not be more susceptible to contracting infections than other people, but are at greater risk because febrile episodes can trigger an adrenal crisis, if not properly treated.

e. Preventive measures

Physicians must inform patients with adrenal insufficiency and their parents / guardians, in the case of minors, of the importance of following social distancing measures and of using PPE in case of community life, in order to prevent infection.

The doctor of the territory (Paediatrician / General Practitioner) and the Local Health Service of competence (as currently indicated by the Competent Authority) must be informed if one or more of the

symptoms suggestive of COVID-19 (fever ≥ 38°C, dry cough, dyspnoea) develop in a patient with adrenal insufficiency. In addition to the symptoms, the particular basic pathology and the followed therapy must be reported. Furthermore, the patient must contact his / her own physician to obtain advice on how to adapt the replacement therapy to the current acute condition unless he/she has already been instructed to increase the dosage independently.

In order to contain the spread of the epidemic during the COVID-19 emergency, routine follow-up visits were deferred in most Italian Paediatric Endocrinology Centres, while retaining the capacity to provide all urgent consultations and the guidance of the treatment in patients with symptoms suggestive of COVID-19.

f. Support of telemedicine systems

The health emergency caused by the COVID-19 pandemic may disrupt routine reference specialist checks. This can occur if the patient is in quarantine or in isolation, or when the rules on social distancing make it impossible for him/her to go to the health facilities for the specialist checks in accordance with the time considered appropriate by the treating specialists.

In some territories, alternative measures have already been activated (e.g. telephone or video calls) to compensate for the reduced capacity of the health system to provide outpatient visits, in order to ensure continuity of care for all paediatric patients with chronic and or rare endocrine diseases.

In some of these clinical events, it is possible to use modern Telemedicine systems to deliver remote medical control services to the patient's home. This can be done by means of video calls, together with the exchange of data and information in digital format that are sent to the doctor directly from the patient or caregiver using software and / or digital medical devices. These technological opportunities can make a significant contribution in the management of continuity of the health care in emergency, if used appropriately within a well-organized care and assistance process in the area. However, the Telemedicine system does not equal Telemedicine technologies, as digital technological innovations alone do not constitute the solution to care problems, being only a means to generate new care strategies and new care services. These methodological aspects are underlined in order to offer healthcare professionals, who deal with patients with adrenal insufficiency, the appropriate scientifically valid points of reference for using these opportunities for the provision of specialist services in an appropriate and safe way.

The definition of the necessary elements for telemedicine services during the COVID-19 emergency is beyond the scope of this work, but more details can be found in the Rapporto ISS COVID-19 n. 12/2020 about interim indications for telemedicine care services during the COVID-19 health emergency (16). Some researchers from COVID-19 Rare Diseases Group also contributed to its implementation.

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Useful links

Società Italiana di Endocrinologia e Diabetologia Pediatrica, SIEDP www.siedp.it

Società Europea di Endocrinologia Pediatrica, ESPE http://www.eurospe.org

Società Europea di Endocrinologia ESE www.ese-hormones.org/

Società Italiana di Pediatria, SIP www.sip.it/

WHO COVID-19 www.who.int/emergencies/diseases/novel-coronavirus-2019

SARS-Co V-2 Infection in children: www.nejm.org/doi/full/10.1056/NEJMc2005073

ENDOERN: https://endo-ern.eu

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