Expert Review of Clinical Immunology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierm20

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To cite this article: Isabella Quinti , Ivano Mezzaroma & Cinzia Milito (2021): Clinical management of patients with primary immunodeficiencies during the COVID-19 pandemic, Expert Review of Clinical Immunology, DOI: 10.1080/1744666X.2021.1873767

To link to this article: https://doi.org/10.1080/1744666X.2021.1873767

Published online: 15 Jan 2021.

EXPERT REVIEW OF CLINICAL IMMUNOLOGY
https://doi.org/10.1080/1744666X.2021.1873767

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REVIEW

Clinical management of patients with primary immunodeficiencies during the COVID-19 pandemic

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ABSTRACT

Introduction: Patients affected by Inborn Errors of Immunity (IEI) represent a potential group-at-risk in the current COVID-19 pandemic. Studies on large and small cohorts of IEI reported a huge variability clinical manifestations associated to SARS-Cov-2, ranging from asymptomatic, mild, moderate/severe to death. A great impulse to improve remote assistance programs and to switch to home-based treatment to reduce mobility and face to face contacts has been implemented.

Areas covered: The authors completed a comprehensive review of the literature by searching the PubMed database for studies on large and small cohorts and case reports of IEI patients with COVID-19, with the aim to provide useful information for their clinical management during the COVID-19 pandemic.

Expert opinion: Surprisingly, a low number of IEI patients affected by SARS-Cov-2 were reported with a risk to die for COVID-19 overlapping that of the general population. The low number might be explained by the choice of most physicians to inform early in the pandemic about safety measures, to switch most of the IEI patients to home therapy and to remote assistance. The guidelines issued by the scientific societies and periodically updated, represent the best tool for the clinical management of IEI patients.

ARTICLE HISTORY
Received 25 November 2020
Accepted 6 January 2021

KEYWORDS
Inborn errors of immunity (IEI); SARS-CoV-2; COVID-19; immunoglobulin replacement; convalescent plasma; remote assistance; home-based treatment; guidelines; virus escape mutants

1. Introduction

SARS-CoV-2 is a novel coronavirus, not encountered before by humans. Thus, everyone is susceptible to infection as the virus rapidly spreads in the current Coronavirus disease 2019 (COVID-19) pandemic. A wide spectrum of clinical expression of SARS-CoV-2 infection occurs, ranging from asymptomatic to mild upper respiratory tract illness, or moderate to severe disease with respiratory distress or multi-organ failure requiring intensive care and organ support to death [1]. This variability of disease severity suggests that the individual immune responses to SARS-CoV-2 play a crucial role in determining the clinical course after first infection. Since primary immune deficiencies, now called Inborn Errors of Immunity (IEI) are congenital disorders of the immune system [2], patients with IEI might represent a potential group-at-risk in the current pandemic of COVID-19. IEI patients have mutation in genes encoding for components of the immune systems required for protection from infections, including COVID-19 [3,4]. Only few studies described COVID-19 in large or small cohorts of patients affected by IEI [5–7]. Here, we revised the main findings extracted from the PubMed search with the aim to provide useful information for the clinical management of IEI patients affected by SARS-Cov-2 infection.

2. Clinical presentation of SARS-Cov-2 infection in patients affected by IEI

Clinical presentation does not differ in IEI patients in comparison with the general population. Two papers addressed the issue of clinical manifestations at onset in two large series of IEI patients. From data described by the IUIS International Collaborative Study on 96 IEI patients with SARS-Cov-2 infection, it appears that IEI patients with SARS-Cov-2 infection presented a spectrum and a frequency of symptoms overlapping that described in the general population with fever (69%), cough, dyspnea (13%) diarrhea (13%), fatigue, and myalgia (16%) [5]. In the IUIs cohort, about 60% of IEI patients were hospitalized. Similar symptoms were reported in a cohort of 16 IEI patients in New York described by Hsi-en Ho et al. who also analyzed the median duration of symptoms (29 days from symptom onset to resolution or death) [6]. According to WHO [8], SARS-Cov-2 positive patients might be stratified in asymptomatic, mild, and moderate/severe COVID-19.

2.1. Asymptomatic and mild

According to IUIS survey [5], 16% of patients who underwent testing for SARS-CoV-2 were asymptomatic, and about 42% of patients had mild symptoms [5]. The asymptomatic/mild course did not appear to be a peculiar characteristic of a given IEI (Table 1) since patients with different diagnoses might be poorly symptomatic even in the presence of preexisting conditions, such as chronic lung disease. Similarly, the majority of patients in the New York cohort that collected 16 patients [6], were either asymptomatic or had only mild disease and promptly recovered despite the presence of co-morbidities. This observation confirms what has been already observed in IEI patients affected by influenza virus infection [9,10].

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Article highlights

- COVID-19 in IEI patients does not appear to be significantly different from the general population with the exception of a younger age, and a longer length of SARS-Cov-2 positivity.
- Most patients with antibody production defects do not experience severe disease.
- Patients with predominantly T cell defects, and defects of innate immunity are under-represented in the reported cohorts preventing an assessment of any correlation with COVID-19 severity.
- Co-morbid conditions appear to be relative rare, but important in determining outcome.
- IEI patients with COVID-19 should be referred to their consultant specialists due to the high variability of COVID-19 presentation even within the same IEI condition.

2.2. Moderate and severe

A clinical progression, was observed in 30% of the entire IUIS cohort with about 13% of patients requiring noninvasive ventilation/oxygen administration, and 17% requiring admission to ICUs for invasive ventilation, including extracorporeal membrane oxygenation. The vast majority of these patients had preexisting comorbidities. Once more, IEI patients admitted to ICU for severe COVID-19 have a wide spectrum of IEI diagnoses (Table 1). Differently from the general population, patients with IEI and severe COVID-19 requiring Intensive Care Unit (ICU) admission were younger.

2.3. Atypical presentation

One patient presented with altered mental status as the primary complaint [6]. A Guillain-Barré syndrome complicating SARS-CoV-2 infection was also described in a patient with selective IgA-deficiency [11]. One patient with severe AIHA required ICU admission [7,8].

2.4. Co-infections

Co-infections identified during the COVID-19 hospitalization included Campylobacter enteritis in a patient with hypogammaglobulinemia, Mycobacterium avium complex lung disease in a patient with IFNGR2 deficiency, and oral candidiasis in a patient with XHIGM. It should be underlined that most patients were treated for potential bacterial co-infection or superinfection with antibiotics and extra immunoglobulin infusion [5–7].

2.5. Mortality

Eleven percent of patients form the IUIS cohort died. One child was affected by X-CGD, concomitant Burkholderia sepsis, and HLH, and one child was affected by severe gut GVHD following HSCT for XIAP deficiency and developed septic shock and HLH. All adult patients with IEI (CVID, isolated IgG deficiency, IgA and IgG2 deficiency) who died had comorbidities (cardiomyopathy, chronic kidney diseases, malignancies, chronic lung and heart diseases, hypertension, and diabetes) [5–7]. A higher mortality was reported in the New York cohort (25%) where all patients who succumbed were adults and all had preexisting PID-associated autoimmune/inflammatory complications, or chronic lung disease, and kidney disease [6].

Table 1. COVID-19 course in IEI patients.

IEI	COVID-19: Asymptomatic/ mild	COVID-19: Moderate/ severe	COVID-19: Fatal
X-linked Agammaglobulinemia	5	3	0
Agammaglobulinemia	1	1	0
Hypogammaglobulinemias	2	1	1
Common Variable Immunodeficiencies	22	10	6
Cytotoxic T lymphocyte–associated protein 4 (CTLA4) deficiency	0	2	0
IgA- IgG2 deficiency	2	1	1
XHIGM	0	1	0
Autoimmune Lymphoproliferative Synrome-like	2	0	0
Wiskott-Aldrich syndrome	1	1	0
Chronic Granulomatous Disease	5	0	1
Combined Immunodeficiencies	5	5	0
X-linked Severe Combined Immunodeficiency (SCID)	1	0	0
Activated PI3 kinase delta (PI3k) syndrome	1	0	0
Phosphoglucomutase 3 (PGM3) deficiency	1	0	0
STAT3 Loss of function (LOF)	2	0	0
Familiar mediterranean fever (MEFV)	2	1	0
Aicardi-Goutieres syndrome	2	1	0
X-linked inhibitor of apoptosis (XIAP) deficiency	0	0	1
IFNGR2 deficiency	0	1	0
Autoimmune Polyendocrine Syndrome type 1 (APS1) or Autoimmune Polyendocrinopathy-Candidiasis -ectodermal dystrophy (APECED)	0	1	0
Prolidase deficiency	0	1	0
Protein kinase D (PRKD) deficiency	1	0	0
Chronic mucocutanous candidiasis	1	0	0
GATA 2 deficiency	1	0	0

3. Diagnosis

3.1. SARS-Cov-2 diagnosis

Testing for serum specific IgG and IgM antibodies might not be useful in patients with IEI in particular in patients with severe hypogammaglobulinemias. For those patients with other forms of IEI this test might be of help. However, as general rule, SARS-Cov-2 infection in IEI patients should be diagnosed by molecular PCR testing of the nasopharyngeal swab only. For those IEI patients who are positive at the molecular testing for SARS-Cov-2, it has been suggested to perform one or more additional molecular PCR testing after the clinical recovery as they might require time to clear the infection [4,6]. In the general population, SARS-Cov-2 positive patients are considered to be without infectious potential beyond day 10 after the onset of symptoms. In contrast, immunocompromised and severe-to-critical patients may have prolonged viral shedding and, thus, may also provide prolonged infectiousness, as observed also by us, and as reported in an XLA patient who had SARS-CoV-2 positive viral culture 7 weeks after onset of COVID-19 [4–7,12]. This

increased length of SARS-Cov-2 positivity might represent a potential risk for virus genetic changes since high rates of mutation might arise, as previously suggested in studies on patients chronically infected with SARS-CoV-2 [13–15] or demonstrated for other viruses such as chronic OPV infections.

3.2. Laboratory data and inflammatory markers

As to what reported in the general population, a significant decline in white blood cells and in particular in total lymphocyte count was observed in IEI patients as well as elevation in systemic inflammatory markers (C-reactive protein, fibrinogen, D-dimer) and cytokines such as serum IL-6 and IL-8, in particular in patients with severe COVID-19. Serum IL-1b was not commonly elevated and TNF-a was elevated in half of patients. Surprisingly, reduced signs of inflammation were observed in patients with XLA [6]. Patients with APS1/APECED as well as IEI patients prone to develop auto-antibodies should be carefully monitored because of the demonstration of neutralizing anti-IFN antibodies in a large number of COVID-19 patients [16].

4. Treatment and management

Therapeutic strategies reflected the wide range of drugs in use in COVID-19 patients even for most of them a proven efficacy has not yet been demonstrated. Treatments administered to IEI patients varied greatly and consisted many medications administered: antibiotics, hydroxychloroquine/chloroquine, systemic steroids, anti-IL6R and anti-IL1R, antivirals, and enoxaparin. Oxygen supplementation was needed in the majority of IEI patients with moderate/severe COVID-19. In addition, few patients received convalescent plasma [5–7].

4.1. Immunoglobulin replacement

Immunoglobulin replacement treatment was continued in all patients described in the literature and it should be continued in all IEI patients [4–7]. Few papers described the beneficial effect of high doses immunoglobulins administered in COVID-19 patients on improving symptoms, fever, and lymphopenia, although the selected patients were not affected by IEI [17]. It has been widely demonstrated that IVIG exert immunomodulatory effects on many inflammatory cells such as monocytes [18] and may also contain antibodies directed to other coronaviruses potentially cross-reactive with COVID-19 [19]. Due to the widespread and long-term circulation of human coronaviruses, and the pooling of plasma from thousands of donors for every lot, immunoglobulins might contain levels of anti-human seasonal coronaviruses antibodies. However, these antibodies did not neutralize the SARS-CoV-2 [20].

Here, it should be mentioned that immunoglobulin treatment is not nowadays, nor it might be in the future, a potential risk of SARS-Cov-2 transmission since virus inactivation and removal steps during the manufacturing process ensure the safety of immunoglobulin therapies. At the moment, however, it did not provide immunity against SARS-Cov-2, and thus IEI patients who do not have antibody deficiency do not require prophylactic immunoglobulin treatment. It will be possible, in the next future, to assist to a shortage of immunoglobulin products due to a decline in plasma supply caused by a drop in blood collection for the personal confinement and movement restriction measures. It is mandatory that IEI enter in a list of priority for immunoglobulin treatment in case of shortage [21]. In addition, plasma industry companies are in the process of producing polyclonal hyper-immune anti-SARS-Cov-2 immunoglobulins, and this might represent a further cause of shortage.

4.2. Convalescent plasma

Although passive transfer of antibody to patients unable to make antibody is a logical strategy, the value of antibody infusion to patients with normal immune systems is a matter of discussion. In COVID-19 patients, a randomized control groups trial recently failed to demonstrate efficacy [22,23]. However, the administration of convalescent plasma may be a useful approach for the treatment of patients whose immune systems have been compromised by both an underlying disease such as IEI, or secondary to B cell depleting therapies, such as anti-CD20 monoclonal antibody therapy [24,25]. However, once more it should be stressed that the use of convalescent plasma, and more recently the use of monoclonal antibody have been considered as potential cause of increase of SARS-Cov-2 escape mutants [13].

4.3. Remote assistance

In the COVID-19 era, e-health has had a great impulse trying to avoid face-to-face assistance without reducing the quality of care and Health-Related Quality of Life (HRQoL) of our patients. Tele-health is a tool for the evaluation of IEI patients to avid as much as possible personal contacts with hospital care systems and in particular with emergency units. At the start of the SARS-Cov-2 pandemic, recommendations by the panel of medical advisers of the Spanish Association of Primary Immune Deficits were issued by suggesting that all adult patients of the IEI module were follow-up by phone at least every second week. All patients were informed to follow the recommendations for confinement issued by the health authorities [26]. Similarly, at the time of the beginning of coronavirus disease 2019 pandemic, we switched the patients attending our center to remote assistance and from hospital-based to homebased immunoglobulin treatment [27]. It is important to underline that the efficacy of this process needs to be monitored over time. By the use of a disease-specific tool [28], and by the use of the 12-item General Health Questionnaire, a generic tool to assess the risk of anxiety/depression [29], we have recently shown that COVID-19 epidemic impacted the HRQoL and the risk of anxiety/depression of adult patients with primary antibody deficiencies. However, we showed that HRQoL was similar in patients forced to shift to home therapy and in patients who continued their usual home-based replacement. In addition, we showed that the remote assistance program based on the use of telephone, social networks by a specific e-mail account was a useful strategy to limit personal contacts without influencing the quality of care [27]. For those IEI patients who need face-to-

face services and for those patients for whom evaluations and interventions are time-sensitive, it was suggested to use clean spaces at hospital or clinic entrances. Face-to-face services might be required for newly identified IEI and for monitoring patients with an established IEI diagnosis for: acute infections; chronic pathologies such as lung chronic diseases; autoimmune phenomena; therapeutic compliance and in particular, beside immunoglobulin replacement, all therapeutically plans for any IEI-associated conditions that should be continued, including chemotherapy for malignancies [30].

5. Guidelines

Together with IPOPI, INGID, APSID, ASID, ARAPID, CIS, LASID, SEAPI, ESID worked on a joint statement to provide guidance in advising patients with primary immunodeficiency under our care in the current COVID-19 context (Joint statement on the current epidemics of new Coronavirus available at www.esid.org) [31]. Recently, an international consensus summarized how to best manage patients with IEI during the pandemic. Precautionary recommendations for patients with IEI follow the national guidelines for the general population and include strict hygiene and social distancing measures to limit exposure [32,33].

6. Conclusions

As in the general population, the clinical impact of COVID-19 in IEIs varies from mild symptoms to death. Surprisingly, from the available data, IEI patients have a risk to develop severe COVID and to die for COVID-19 overlapping that of the general population. Those with a more severe COVID-19 have comorbidities or complications of their immunodeficiency. However, despite several comorbidities, most of them present a milder course of the disease or are even asymptomatic. Some differences might be peculiar of IEI patients and in particular, the younger age, and the longer length of SARS-Cov-2 positivity, even if some of these conditions might be observed even in the general population of non-immunocompromised subjects. The stratification of IEI patients into the different degrees of COVID-19 severity has not allowed so far, to identify a given IEI entity as responsible for an increased risk of contracting a serious form of COVID-19 or of dying from it. As an example, despite we and others [5,7] have reported that patients with agammaglobulinemia who lack B lymphocytes showed milder course of disease as compared to patients with other forms of defects of antibody production such as CVID, this observation could not be confirmed by others [12]. Most IEI cases are under immunoglobulin replacement. Speculation is that immunoglobulin therapy might help to modulate the immune response to SARS-Cov-2 by their effect on inflammatory cells such as monocytes and macrophages. Likewise, other treatments might have contributed to a mild COVID-19 course such as IL-1 blockade administered to patients with auto-inflammatory diseases, and JAK inhibitors administered to patients with interferonopathies [5].

7. Expert opinion

The low number of IEI patients affected by COVID-19 does not allow for now to draw any conclusion concerning treatment guidelines for IEI patients with COVID-19. Additional studies are in progress to identify IEI defective humoral and cellular immune responses to SARS-Cov-2. This unexpected low number of IEI patients affected by COVID-19 observed might be explained by:

(a) the choice of most physicians taking care of IEI patients to inform early in the pandemic about safety measures, to switch most of them to home therapy and to remote assistance. In this sense, guidelines, promptly issued by the scientific societies and periodically updated, represent the best tool for the clinical management of patients affected by IEI [4,30–32];

(b) the continuous patients' educations on protection procedures all IEI patients have been following since their diagnosis;

c) to underreporting, even if this might not be the case since immunological societies and patients' organizations started their surveys already in the early phases of the pandemic. However, the limited number of patients reported in the literature does not explain the paradox of a mild and even asymptomatic course of SARS-Cov-2 infection in IEI patients, despite many of them suffer from comorbidities, and in particular from chronic lung disease. In this sense, patients affected by IEI might be informative for the general population. It should be noted here that for now we might only speculate on some preliminary observations. As an example, we reported our experience on a patient affected by autosomal recessive agammaglobulinemia who underwent in the past to right lung excision [7]. He was infected by SARS-Cov-2 infection, but he remained asymptomatic without any signs of additional lung involvement, even if his swab continued to be positive for SARS-Cov-2 for more than 3 weeks. We exchanged this experience with the colleagues of the Italian Network for Primary Immunodeficiency and we identified additional asymptomatic or pauci-symptomatic XLA and agammaglobulinemic patients [7]. Due to the lack of B cells in these patients, we speculated on a possible harmful role of B cells in COVID-19 pathogenesis. This was further supported by the demonstration that patients under anti-CD20 treatment had a mild COVID-19 [33], as well as patients under BTK inhibitors [34]. However, our hypothesis was argued since other agammaglobulinemic patients later reported in the literature showed an aggressive COVID-19 disease [12]. However, these agammagglobulinemic patients with a more aggressive COVID-19 were treated with convalescent plasma. The Authors concluded stressing the potential benefit of this treatment while others still debate on the potential risk to induce the emergence of resistant strains. Thus, it should be mentioned here that each IEI patient represents a unique in that the COVID-19 clinical expression varies also within the same IEI entity, as we knew form many other co-morbidities, our patients faced during their life. Further efforts are in progress to define the clinical course of SARS-Cov-2 in IEI patients. In addition, work is in progress to identify new IEI diagnoses in patients healthy until the time they developed SARS-Cov-2

infection [35]. Only large collaborative studies still ongoing might give insight on SARS-Cov-2 infection, COVID-19 treatments, and on response to the new vaccines since patients affected by IEI might always represented a fundamental group to understand the pathogenic mechanisms underlying most infectious and inflammatory diseases.

Acknowledgments

We thank all MD, nurses, and health personnel taking care of COVID-19 patients over the world.

Funding

This paper was funded by Progetto Ateneo Sapienza, 2020.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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