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Clinical impact and disease evolution of SARS-CoV-2 infection in familial Mediterranean fever

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ABSTRACT

The innate immune system is critically involved in the pathogenesis of familial Mediterranean fever (FMF), characterized by dysregulated inflammasome activity and recurrent inflammatory attacks: this is the most common among monogenic autoinflammatory diseases, which shares some biochemical pathways with the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection. In this short review we explore the overlap in the pathophysiology of FMF and SARS-CoV-2 infection, discussing how to understand better the interaction between the two diseases and optimize management. A poorer outcome of SARS-CoV-2 infection seems not to be present in infected FMF patients in terms of hospitalization time, need for oxygen support, need for intensive care, rate of complications and exitus. Long-term surveillance will confirm the relatively low risk of a worse prognosis observed so far in SARS-CoV-2-infected people with FMF. In these patients COVID-19 vaccines are recommended and their safety profile is expected to be similar to the general population.

1. Introduction

Highly heterogeneous is the clinical course of the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection, which can give rise to a wide spectrum of symptoms, from very mild to dramatically severe, such as acute respiratory distress syndrome (ARDS), multiorgan failure and cytokine storm syndrome (CSS), burdened by a poor outcome [1]. Causes underlying this different evolution are not fully elucidated, though they seem related to hyper-reactivity of the immune system, abnormally prolonged inflammatory response and delayed viral clearance [2]. The pathogenetic mechanism of SARS-CoV-2 includes three phases of entry into the target cell: the binding phase of viral spike (S) protein to angiotensin-converting enzyme 2 (ACE2), the proteolytic phase of the S protein catalyzed by cell transmembrane serine protease 2 (TMPRSS2) and the fusion phase of viral particle with the host cell membrane [3,4]. Within the host cell, the single-stranded RNA (ssRNA) genome of SARS-CoV initiates replication and cytoplasmic accumulation; the host innate immune system recognizes ssRNA or its double-stranded intermediate and becomes active, leading to an initial antiviral response through the production of type 1 interferons (IFNs) and secretion of proinflammatory cytokines. Patients who progress to the second phase show a strong immunological and hyperinflammatory response that is defined as a "cytokine storm" and that can lead to worsening respiratory symptoms and severe clinical pictures; some of these patients remain unresponsive to treatment and are at a higher risk of complications which may be fatal [5].

A similar hyperinflammatory state is the pivotal feature of febrile attacks occurring in patients with familial Mediterranean fever (FMF), an autoinflammatory disease caused by gain-of-function mutations in the *MEFV* gene which encodes pyrin, an innate immunity sensor

Abbreviations: FMF, familial Mediterranean fever; SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2; ARDS, acute respiratory distress syndrome; CSS, cytokine storm syndrome; ACE2, angiotensin-converting enzyme 2; TMPRSS2, transmembrane serine protease 2; ssRNA, single-stranded RNA; IFN, interferon; IL, interleukin; RhoA, Ras homolog family member A; GTPase, guanosine triphosphatase, COVID-19, COronaVIrus Disease 2019; NLRP3, NLR pyrin domain containing 3; TNF, tumor necrosis factor; MCP-1, monocyte chemoattractant protein-1; GM-CSF, granulocyte-macrophage colony-stimulating factor; JAK-STAT, Janus kinase-signal transducer and activator of transcription; CRP, C-reactive protein; SAA, serum amyloid-A; CT, computed tomography.

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detecting bacterial toxin-induced RhoA (Ras homolog family member A) GTPase (guanosine triphosphatase) inactivation [6,7]. However, the specific trigger of febrile attacks in FMF and the possible metabolic pathways involved in mediating their pathogenesis remain roughly understood. To date, whether the dysregulated innate immunity of FMF patients could be protective versus the SARS-CoV-2 infection or harmful is unestablished. The first-line drugs in the treatment of FMF, colchicine and interleukin-1 (IL-1) antagonists, have a proven and well-established efficacy in controlling FMF hyperinflammatory reactions, but may also protect against the development of a severe 'COronaVIrus Disease 2019' (COVID-19), due to their modulating action on the cytokine storm [8]. There are still few studies regarding the course of COVID-19 in auto-inflammatory diseases. The main goal of this review is to describe the mechanisms underlying the development of different clinical sceneries and outcomes of SARS-CoV-2 infection in FMF through a medical literature search for the most relevant studies exploring this association.

2. COVID-19 outbreak raging around the world

Coronaviruses are a variety of viruses that cause mild-to-severe respiratory infections in humans, but at the end of 2019 a novel enveloped RNA coronavirus, named SARS-CoV-2, emerged from Wuhan in China: since then, this easily-transmissible pathogenic coronavirus has provoked an acute respiratory disease of variable severity, which has rapidly spread throughout our planet, becoming a worldwide public health emergency. The most commonly recognized COVID-19 symptoms are fever, dry cough and shortness of breath; radiographic and laboratory abnormalities as lymphopenia and elevated lactate dehydrogenase are common, but nonspecific [9]. There is partial knowledge about the tendency to deterioration of COVID-19, but mostly why some patients develop CSS, a dramatic cascade of cytokine activation with overwhelming systemic inflammation, hemodynamic instability and multiple organ failure, is actually unknown. The structural S protein of the SARS-CoV-2 binds the ACE2 receptor on different target cells, such as vascular endothelial cells, lung pneumocytes and bronchial epithelial cells, but the diverse expression of ACE2 in people may influence both the susceptibility to disease and severity of COVID-19 [10]. After attaching epithelial cells in the respiratory tract, SARS-CoV-2 starts replicating and migrating down to the deepest airways, entering alveolar cells of the lung; host proteases, such as TMPRSS2, cathepsin L and furin, participate in the cleavage of the S protein and virus entry into cells. After the interaction with the ACE2 receptor, SARS-CoV-2 is endocytosed and interacts with Toll-like receptors in the endosome: this interaction promotes type I IFN-response and increases the expression of proinflammatory cytokines via nuclear factor-κB. Furthermore, the replication of SARS-CoV-2 triggers a strong immune response through the stimulation of the NLR pyrin domain containing 3 (NLRP3) inflammasome, supporting the release of multiple NLRP3-induced mediators, typical of innate immunity, such as IL-1 [11]. There is urgent need to develop rapid, sensitive and specific methods for monitoring cytokines in infected patients with point-of-care testing that might provide help in early COVID-19 diagnosis and management, as SARS-CoV-2 infection can lead to dramatically severe pneumonia and ARDS, requiring support with mechanical ventilation in 10–20% of hospitalized patients [12].

COVID-19 may be scholastically subdivided into a symptomatic and non-symptomatic disease: the first one has been classified into four types: mild, moderate, severe and critical, leading to respiratory symptoms of increasing severity. Loss of smell and taste sensations are also described as additional symptoms in adults, but are less common in the pediatric age. Conversely, vomiting, diarrhea and abdominal pain are frequent and variably associated with respiratory symptoms. Heart failure, sepsis and septic shock can be found in the critical stage of the disease [13]. It has been widely reported that children without any underlying conditions, like chronically impaired lung function or immunosuppression tend to experience a milder COVID-19: the exact reasons are actually undeciphered, though probably related to a lower pollution exposure and less frequent coexistence of comorbidities such as diabetes and hypertension [14]. In addition, a peculiar local microbiome and potential co-infections in the nasopharyngeal tract may cooperate to a more effective overrun of SARS-CoV2 infection in the pediatric patient [15]. Furthermore, the innate immune responses are more vigorous and workable in younger patients, who show early polyclonal B cell response with production of plasmablasts, mostly of IgM isotype, and have the ability to produce natural antibodies with broad reactivity that have not yet been selected and shaped by the reaction to common environmental pathogens [16].

3. The induction of an immune-mediated cytokine network

The cytokine storm observed in COVID-19 is the result of uncontrolled immune activation which generates different sceneries of hyperinflammation evolving to multi-organ disease or, if inadequately treated, to multi-organ failure [17]. Three criteria have been recognized to define the "cytokine storm" occurring in many conditions as COVID-19, other viral infections, sepsis or cancer: (a) symptoms of acute systemic inflammation, (b) increased level of circulating cytokines, and (c) secondary organ dysfunction [18]. Understanding the pathogenesis of CSS may help unravel not only risk factors for the condition, but also therapeutic strategies to modulate the immune response and deliver improved outcomes in COVID-19 patients at higher risk for severe disease. The amplification of host immune response fuels the cytokine storm, which is characterized by the massive release of a wide range of acute-response cytokines (tumor necrosis factor, TNF, and IL-1) and chemotactic cytokines (monocyte chemoattractant protein-1, MCP-1, and IL-8), combined with IFN-γ, IL-18 and IL-6. IL-6 binds to either membrane bound IL-6 receptor or soluble IL-6 receptor, forming a complex that acts on gp130, regulates levels of IL-6, MCP-1 and granulocyte-macrophage colony-stimulating factor (GM-CSF) via Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway and thereby perpetuates the inflammatory process. IL-6, along with other pleiotropic cytokines, drives an acute phase response that elevates serum ferritin, complement, C-reactive protein (CRP) and procoagulant factors, many of them measurable through blood tests. The acute phase response of cytokine storm is relatively over-exaggerated. Since high serum levels of cytokines are inversely related to the total lymphocyte count, low levels of cytotoxic T cells may contribute to a reduced viral clearance [19]. This markedly high level of chemokines attracts many inflammatory cells, like neutrophils and monocytes, causing a diffuse, sometimes massive, infiltration into the lungs and other involved tissues. Such an intense proinflammatory cytokine/chemokine imbalance reflecting the very rapid viral replication is also responsible for the induction of apoptosis in lung epithelial and endothelial cells through mechanisms implicating the Fas-Fas ligand apoptotic pathway [20]. As a consequence, lung epithelial cell barriers are disrupted and result in a vascular leakage with alveolar edema leading to hypoxia [21]. Blocking upstream events related to or at the level of cytokine response, such as JAK-STAT signaling of macrophages to reduce IL-1 and IL-6 production, offers a potential therapeutic target for the cytokine storm. Patients with severe COVID-19 also display a proinflammatory cytokine signature, following higher plasma concentrations of TNF, fibroblast growth factor, GM-CSF, IL-1, IL-1 receptor antagonist, IL-7, IL-8, IL-10, MCP-1, vascular endothelial growth factor and platelet-derived growth factor [22]. Clinically, most patients with CSS are febrile and display fatigue, anorexia, headache, skin rash, diarrhea, arthralgia, myalgia, and even neuropsychiatric findings: all these symptoms largely depend on the cytokine-induced tissue damage [23]. Disseminated intravascular coagulation may be seen as a progression of CSS combined with both hypotension and vasogenic shock. The most severe cases also develop cardiomyopathy or renal and liver acute failure, which impact severely on the overall prognosis [24].

4. The protean face of familial Mediterranean fever

Patients with FMF have periodic fevers and episodic serositis which recur over time: the disease onset is usually in childhood, with most patients (approximately 60%) experiencing their first symptoms before 10 years [25]. This disease, caused by mutations in the *MEFV* gene located on the chromosome 16p13.3, codifying for the pyrin protein, is more frequently found among non-Ashkenazi Jews, Arabs, Armenians and Turks [26,27]. Abdominal FMF attacks resemble the clinical presentation of 'acute abdomen', but symptoms resolve spontaneously [28]. Although FMF and other familial periodic fever syndromes were discovered in the second half of the 20th century, reports of these conditions yet unidentified date back to a more remote past [29,30]. FMF has complex genetic interactions, and only 55.7 % of *MEFV* variants display a substantial clinical impact, with 1/3 being represented by variants of uncertain significance [31]. Since FMF is an autosomal recessive condition, it was initially assumed that mutations led to a loss of the protein function; however, experiments with mice expressing the truncated form of pyrin failed to recapitulate the typical FMF picture. On the basis of experiments on pyrin-deficient and 'knock-in' mice it was found that disease-causing *MEFV* mutations result in a pyrin gain-of-function and that disease expression is dependent on the amount of the mutated protein produced. This might also explain why the heterozygous state in FMF patients may be sometimes associated with a clinically relevant disease [32]. Pyrin acts as a pattern recognition receptor sensing inactivation of GTPase in response to bacterial toxins and/or effectors that inactivate RhoA, being involved in the regulation of inflammation, apoptosis and IL-1 processing [33]. Park et al. demonstrated that pyrin is normally inactive, but that *MEFV* mutations promote a constitutive pyrin activation, resulting in overload of proinflammatory cytokines [34].

FMF clinical attacks consist of brief recurrent episodes of fever with different inflammatory signs, ranging from mild to incapacitating, and are challenging to recognize in toddlers or children: most attacks occur irregularly, last 1-to-3 days and subside in a spontaneous fashion, although physical and emotional stresses or menses may be triggers [35]. Abdominal pain is largely present in the febrile attacks of patients with FMF [36]. Chest pain may be due to pleural or sub-diaphragmatic inflammation, but may even involve the pericardium [37]. The most ominous and potentially lethal complication of FMF is secondary amyloidosis, which more frequently affects the kidney as a result of tissue deposition of amyloid, a proteolytic cleavage product of the acute phase reactant serum amyloid-A (SAA) [38]. Laboratory tests performed during FMF attacks show increased parameters of inflammation with high SAA, high CRP, leukocytosis, thrombocytosis as well as high fibrinogen and immunoglobulins in the serum. Diagnosis of the disease is clinical, though supported by *MEFV* gene mutation analysis, even if specific variant interpretation may be required: a first step is to review carefully all details of febrile attacks, since examination between flares is usually unrevealing, and tailor the potentially laboratory assessment to a few tests focusing on FMF, such as a favorable response to colchicine [39]. Supportive measures are required during attacks, but the mainstay of FMF management is long-term prophylaxis with colchicine [40]. Colchicine is being used in the treatment of FMF since 1972 and is effective in preventing attacks via inhibition of microtubule polymerization of the cytoskeleton and direct inhibition of inflammasome activity; however, further long-term data have confirmed the efficacy of anti-IL-1 treatment in colchicine-resistant patients [41]. The chronic systemic inflammation in FMF can result in damage to multiple organs, and instruments to quantify this damage in individual patients and compare disease outcomes in clinical studies have been recently disseminated [42]. The general course of COVID-19 in patients with FMF is a matter of huge interest since FMF febrile attacks share some similarities with COVID-19-related cytokine storm.

5. The clinical course of COVID-19 in familial Mediterranean fever

The exact role of *MEFV* mutations displaying a propensity to hyperactive innate immunity against COVID-19 is unknown. There have been different experiences reported so far. For instance, the clinical evolution of SARS-CoV-2 infection has been assessed in 342 French FMF patients living in an endemic area near Paris: they were invited to answer a short questionnaire after a phone call or email about a possible SARS-CoV-2 infection during the time span ranging from March 2020 until May 2020; 342 patients answered the survey and diagnosis of COVID-19 was made if the patient displayed clinical symptoms, positive SARS-CoV-2 reverse transcriptase-polymerase chain reaction pharyngeal test, positive serology or typical pathologic features on the chest computed tomography (CT) scan. Overall, 27 FMF patients contracted the virus (7.8 % of the responders) and 315 did not. All but 1 of the FMF-COVID-19 positive patients were taking daily colchicine since a mean time of 23 years; 4 were also receiving an IL-1 inhibitor. Out of the 27 COVID-positive patients, 7 were admitted to hospital, 6 required oxygen supply, and 3 developed ARDS requiring intensive care in terms of mechanical ventilation and/or hemodialysis. Out of the 3 FMF patients who had amyloidosis, 2 were hospitalized and 1 died. At the end of the first epidemic wave in the Paris area, the 5 survivors after hospitalization went back home. Therefore, a worse outcome was found only in FMF patients with known risk factors such as chronic kidney disease, hypertension or obesity, and the authors concluded that FMF treated with long-term colchicine prophylaxis did not add any additional risks for a most severe disease course of SARS-CoV-2 infection in comparison with the general population [43].

Another Turkish multicenter cross-sectional study involving 822 FMF patients with a mean age of 36 years and a mean disease duration of 9 years aimed to evaluate the impact of COVID-19 in FMF during the period June 2020-February 2021; all patients were on colchicine prophylaxis, though 108 of them were not totally compliant. Conversely, 128 patients were colchicine-resistant. The result of the study showed that 59 patients (7 % of the whole cohort) had a COVID-19 diagnosis confirmed by pharyngeal test or chest CT findings; 12 of them were hospitalized and 4 required oxygen support. COVID-19-related complications were observed in only 2 patients (thromboembolism in one, ARDS in the other). No death occurred. In the comparison of demographic details, disease features and COVID-19 outcomes between hospitalized and non-hospitalized patients, it was found that hospitalized ones were significantly older than non-hospitalized (51 versus 31 years, respectively; $p = 0.002$). There was no difference regarding allele frequencies of *MEFV* mutations between hospitalized and non-hospitalized patients. Unlike other previous studies that showed higher rates of oxygen support and mortality among patients with rheumatologic diseases with COVID-19, this study revealed that only older age represented a risk factor in COVID-19-related hospitalization for FMF patients [44].

In an observational study by Haslak et al., 404 young patients with autoinflammatory diseases were enrolled via web-based survey investigating their disease findings due to SARS-CoV-2 infection. In particular, 364 patients had FMF (90 % of the total) being on colchicine prophylaxis; the IL-1 inhibitors anakinra and canakinumab had been used and were still used by 4 and 21 of them, respectively. Twenty-four out of the whole cohort with autoinflammatory diseases were admitted to the hospital due to suspicion of COVID-19 and 20 of them had FMF; 6 FMF patients were on colchicine and had a positive pharyngeal test; none of them were receiving biologic drugs. There were 5 patients with symptoms suggestive of COVID-19 (fever, dry cough, sore throat): 4 had been treated for COVID-19 and were followed-up via outpatient clinic assessments or phone calls; only 1 symptomatic patient was hospitalized for a total of 5 days. All of the confirmed cases recovered completely. The conclusion of the study was that young patients receiving colchicine may not have an increased risk of poorer outcome after SARS-CoV-2

infection. Therefore, rheumatologists should warn their patients not to withdraw the daily routine treatment of their underlying auto-inflammatory illness [45].

In a retrospective Turkish study made by Güven et al., a total number of 496 FMF patients was evaluated; among these, 34 were positive for SARS-CoV-2 at the pharyngeal test and their median age was 40,5 years. At least one comorbidity was found in 64,7 % of cases, mostly hypertension (in 23,5 %). More than 85 % of patients was on colchicine prophylaxis, while 17,6 % was receiving also anakinra. Regarding outcome, 8 out of the 34 patients (23,5 %) were hospitalized, but only 1 was admitted to the intensive care unit and died thereafter (death was attributed to the several comorbidities affecting this patient). The results of the study showed both similar mortality and hospitalization rates in FMF patients and non-FMF patients, while the frequency of comorbidities, proteinuria and use of IL-1 inhibitors were found to be higher in the hospitalized ones [46].

An Israeli study did not find any statistical difference in the hospitalization rate for COVID-19 between the group of FMF patients and non-FMF ones: the authors supposed that neither genetics of FMF, nor colchicine could frankly provide a solid protection against hospitalization for COVID-19 [47]. This theory was in contrast with the preliminary results of the COLCORONA study, in which colchicine seemed to reduce the rate of both death and hospitalizations among non-hospitalized patients with COVID-19 [48]. Similarly, the prospective randomized open-label controlled GRECCO-19 study found that COVID-19 patients receiving colchicine in addition to the standard therapy had a longer time prior to clinical deterioration [49].

Among smaller experiences, Nas et al. found that colchicine positively affected the prognosis of COVID-19 in 3 patients with FMF [50]. Furthermore, Kobak hypothesized that colchicine could have induced a milder clinical presentation of COVID-19 in a 36-year-old obese and hypertensive FMF patient who had been using colchicine since 2008 [51]. Analogously, a meta-analysis has suggested a mortality benefit with colchicine when used in the treatment of COVID-19 patients [52]. Table 1 shows the most relevant outcome results in FMF patients who have been diagnosed with SARS-CoV-2 infection.

Table 1
Outcomes reported for FMF patients diagnosed with SARS-CoV-2 infection.

	Outcomes	*References*
FMF patients under treatment (colchicine or biological therapies)	No reported additional risk of severe COVID-19	[43,45]
	Increased risk of hospitalization for COVID-19 in the oldest patients	[44]
	Increased risk of severe COVID-19 in patients with proteinuria who are on treatment with IL-1 inhibitors	[46]
	No significant differences in terms of hospitalization rate if compared with the general population	[47]
	Colchicine prophylaxis positively affects the overall prognosis	[50,51]

6. COVID vaccination in patients with familial Mediterranean fever

Since December 2020, the first anti-COVID vaccines have been authorized and the vaccination campaign has been opened to the whole population [53]. Although a degree of protection could be offered by the hyperinflammatory state [54], vaccination against COVID-19 is recommended also in patients with FMF. There is no reason to expect more frequent and/or severe adverse events following vaccination against COVID-19 in these patients. In a recent study, it has been shown that 138 doses of COVID-19 vaccine had been administered to 130 patients with inflammatory diseases [55]. Side effects were reported after 71 of 138 (51.4 %) administrations and were consistent with a flare of the underlying disease in 26 of 138 (18.8 %) instances. No serious adverse events or hospital admissions were reported after vaccination. These data, including the largest published series of patients on anti-IL-1/6 biologics to receive any adenoviral vector or mRNA vaccine, show no serious early concerns regarding vaccination and will provide an urgently needed resource to inform decision-making of these patients and their clinicians [55]. Similar results were observed in a large population of immunosuppressed patients, including a cohort of patients with FMF, showing that mRNA vaccines against COVID-19 lead to development of antibodies in immunosuppressed patients without considerable side effects or induction of disease flares [56].

7. Discussion and conclusive remarks

The FMF mutant pyrin fosters inflammasome activation and results in IL-1 oversecretion, which is largely responsible for its clinical effects, i.e. recurrent attacks of sterile inflammation. Similarly, COVID-19 is associated with cytokine dysregulation, increased release of IL-1, TNF, IL-6, different chemokines and higher risk of CSS. The avoidance of hypercytokinemia is a pivotal therapeutic arm in COVID-19, and this aim is also concurrently crucial in the treatment of many auto-inflammatory diseases, such as FMF. Colchicine, which inhibits the recruitment of neutrophils by blocking the cytoskeleton assembly and inhibits inflammasome activation, is the standard therapeutic drug in FMF and has the power to stop the cytokine release. Indeed, multiple FMF patients have been reported to develop SARS-CoV-2 infection, but those regularly receiving colchicine prophylaxis have not manifested severe consequences of the infection. A possible explanation of the lower incidence and milder clinical course of COVID-19 in FMF might be related to *MEFV* mutations displaying a favorable effect against highly contagious diseases, such as the plague, or lethal infections such as the tuberculosis, cholera and malaria [57,58]. These findings support the hypothesis that selective pressures due to infectious disease may have caused functional evolution of pyrin in humans and that *MEFV* mutations, as seen in FMF, may represent the reappearance of an ancestral amino acid state [59].

In conclusion, even though prospective randomized controlled trials are needed, we can prudently state that the dysfunction of innate immune system of FMF does not seem a risk factor for the development of severe COVID-19 and that FMF patients are not at a higher risk for developing life-threatening COVID-19 consequences compared to the general population. In these patients COVID-19 vaccines are recommended and their safety profile is expected to be similar to the general population.

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CRediT authorship contribution statement

FM: Resources, Investigation, Writing - original draft., **CC**: Resources, Investigation, Writing - original draft., **AT**: Resources, Investigation, Writing - original draft., **DR**: Conceptualization, Writing - review & editing. **SE**: Formal analysis, Funding acquisition, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] S. Esposito, M. Gnocchi, M. Gagliardi, P. Affanni, L. Veronesi, M.E. Colucci, C. Neglia, A. Argentiero, N. Principi, Therapeutic strategies against COVID-19, Acta Biomed. 91 (3) (2020), e2020038.

[2] W.J. Wiersinga, A. Rhodes, A.C. Cheng, S.J. Peacock, H.C. Prescott, Pathophysiology, transmission, diagnosis and treatment of Coronavirus disease 2019 (COVID-19): a review, JAMA 324 (8) (2020) 782–793.

[3] Y. Cao, L. Li, Z. Feng, S. Wan, P. Huang, X. Sun, F. Wen, X. Huang, G. Ning, W. Wang, Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations, Cell Discov. 6 (2020) 11.

[4] M. Hoffmann, H. Kleine-Weber, S. Schroeder, N. Krüger, T. Herrler, S. Erichsen, T. S. Schiergens, G. Herrler, N.H. Wu, A. Nitsche, M.A. Müller, C. Drosten, S. Pöhlmann, SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor, Cell 181 (2) (2020) 271–280, e8.

[5] K. Yu, J. He, Y. Wu, B. Xie, X. Liu, B. Wei, H. Zhou, B. Lin, Z. Zuo, W. Wen, W. Xu, B. Zou, L. Wei, X. Huang, P. Zhou, Dysregulated adaptive immune response contributes to severe COVID-19, Cell Res. 30 (9) (2020) 814–816.

[6] A. Stella, M. Lamkanfi, P. Portincasa, Familial Mediterranean fever and COVID-19: friends or foes? Front. Immunol. 11 (11) (2020), 574593.

[7] A. Livneh, P. Langevitz, D. Zemer, S. Padeh, A. Migdal, E. Sohar, M. Pras, The changing face of familial Mediterranean fever, Semin. Arthritis Rheum. 26 (3) (1996) 612–627.

[8] T. Welzel, S.D. Samba, R. Klein, J.N. van den Anker, J.B. Kuemmerle-Deschner, COVID-19 in autoinflammatory diseases with immunosuppressive treatment, J. Clin. Med. 10 (4) (2021) 605.

[9] D.C. Fajgenbaum, C.H. June, Cytokine storm, N. Engl. J. Med. 383 (23) (2020) 2255–2273.

[10] Y. Li, Q. Xu, L. Ma, D. Wu, J. Gao, G. Chen, H. Li, Systematic profiling of ACE2 expression in diverse physiological and pathological conditions for COVID-19/SARS-CoV-2, J. Cell Mol. Med. 24 (16) (2020) 9478–9482.

[11] D. Ragab, H. Salah Eldin, M. Taeimah, R. Khattab, R. Salem, The COVID-19 cytokine storm; what we know so far, Front. Immunol. 11 (2020) 1446.

[12] E. Fan, J.R. Beitler, L. Brochard, C.S. Calfee, N.D. Ferguson, A.S. Slutsky, D. Brodie, COVID-19-associated acute respiratory distress syndrome: is a different approach to management warranted? Lancet Respir. Med. 8 (8) (2020) 816–821.

[13] M.J. Cummings, M.R. Baldwin, D. Abrams, S.D. Jacobson, B.J. Meyer, E. M. Balough, E.M. Balough, J.G. Aaron, J. Claassen, L.E. Rabbani, J. Hastie, B. R. Hochman, J. Salazar-Schicchi, N.H. Yip, D. Brodie, M.R. O'Donnell, Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study, Lancet 395 (10239) (2020) 1763–1770.

[14] P. Brodin, Why is COVID-19 so mild in children? Acta Paediatr. 109 (6) (2020) 1082–1083.

[15] C.M. Hedrich, COVID-19 - Considerations for the paediatric rheumatologist, Clin. Immunol. 214 (2020), 108420.

[16] R. Carsetti, C. Quintarelli, I. Quinti, E. Piano Mortari, A. Zumla, G. Ippolito, F. Locatelli, The immune system of children: the key to understanding SARS-CoV-2 susceptibility? Lancet Child Adolesc. Health 4 (6) (2020) 414–416.

[17] J.N. Gustine, D. Jones, Immunopathology of hyperinflammation in COVID-19, Am. J. Pathol. 191 (1) (2021) 4–17.

[18] Y.M. Gao, G. Xu, B. Wang, B.C. Liu, Cytokine storm syndrome in coronavirus disease 2019: a narrative review, J. Intern. Med. 289 (2) (2021) 147–161.

[19] S. Bhaskar, A. Sinha, M. Banach, S. Mittoo, R. Weissert, J.S. Kass, S. Rajagopal, A. R. Pai, S. Kutty, Cytokine storm in COVID-19-immunopathological mechanisms, clinical considerations, and therapeutic approaches: the REPROGRAM consortium position paper, Front Immunol. 11 (2020) 1648.

[20] B. Hu, S. Huang, L. Yin, The cytokine storm and COVID-19, J. Med. Virol. 93 (1) (2021) 250–256.

[21] H. Sunkara, S.M.R. Dewan, Coronavirus disease-2019: a review on the disease exacerbation via cytokine storm and concurrent management, Int. Immunopharmacol. 99 (2021), 108049.

[22] Q. Ye, B. Wang, J. Mao, The pathogenesis and treatment of the 'cytokine storm' in COVID-19, J. Infect. 80 (6) (2020) 607–613.

[23] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Z. Cheng, T. Yu, J. Xia, Y. Wei, W. Wu, X. Xie, W. Yin, H. Li, M. Liu, Y. Xiao, H. Gao, L. Guo, J. Xie, G. Wang, R. Jiang, Z. Gao, Q. Jin, J. Wang, B. Cao, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (10223) (2020) 497–506.

[24] B. Long, W.J. Brady, A. Koyfman, M. Gottlieb, Cardiovascular complications in COVID-19, Am. J. Emerg. Med. 38 (7) (2020) 1504–1507.

[25] S. Ozen, Update in familial Mediterranean fever, Curr. Opin. Rheumatol. 33 (5) (2021) 398–402.

[26] R. Manna, D. Rigante, Familial Mediterranean fever: assessing the overall clinical impact and formulating treatment plans, Mediterr. J. Hematol. Infect. Dis. 11 (1) (2019), e2019027.

[27] D. Rigante, A systematic approach to autoinflammatory syndromes: a spelling booklet for the beginner, Expert Rev. Clin. Immunol. 13 (6) (2017) 571–597.

[28] R. Manna, D. Rigante, The everchanging framework of autoinflammation, Intern. Emerg. Med. 16 (7) (2021) 1759–1770.

[29] D. Rigante, G. Lopalco, A. Vitale, O.M. Lucherini, C. De Clemente, F. Caso, G. Emmi, L. Costa, E. Silvestri, L. Andreozzi, F. Iannone, M. Galeazzi, L. Cantarini, Key facts and hot spots on tumor necrosis factor receptor-associated periodic syndrome, Clin. Rheumatol. 33 (9) (2014) 1197–1207.

[30] S. Esposito, B. Ascolese, L. Senatore, S. Bosis, E. Verrecchia, L. Cantarini, D. Rigante, Current advances in the understanding and treatment of mevalonate kinase deficiency, Int. J. Immunopathol. Pharmacol. 27 (4) (2014) 491–498.

[31] S. Richards, N. Aziz, S. Bale, D. Bick, S. Das, J. Gastier-Foster, W.W. Grody, M. Hegde, E. Lyon, E. Spector, K. Voelkerding, H.L. Rehm, ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American college of medical genetics and genomics and the association for molecular pathology, Genet. Med. 17 (5) (2015) 405–424.

[32] T.K. Hoang, D.A. Albert, Novel presentations of periodic fever syndromes: discrepancies between genetic and clinical diagnoses, Eur. J. Rheumatol. 6 (1) (2019) 12–18.

[33] D. Rigante, Phenotype variability of autoinflammatory disorders in the pediatric patient: a pictorial overview, J. Evid. Based Med. 13 (3) (2020) 227–245.

[34] Y.H. Park, G. Wood, D.L. Kastner, J.J. Chae, Pyrin inflammasome activation and RhoA signaling in the autoinflammatory diseases FMF and HIDS, Nat. Immunol. 17 (8) (2016) 914–921.

[35] D. Rigante, When, how, and why do fevers hold children hostage? J. Evid. Based Med. 13 (1) (2020) 85–88.

[36] H. Bodur, F.G. Yurdakul, H.F. Çay, Ü. Uçar, Y. Keskin, B. Sargın, G. Gürer, O. V. Yurdakul, M. Çalış, H. Deveci, Y. Aydın, S. Hizmetli, R. Çevik, A.Y. Karahan, I. Sunar, M.T. Duruöz, H. Ecesoy, Z. Günendi, M. Toprak, N. Şen, D. Altıntaş, A. K. Cengiz, G. Çağlayan, A.N. Demir, H. Kaplan, S. Ketenci, M.A. Melikoğlu, M. Nayimoğlu, K. Nas, A.B. Sarıfakıoğlu, I. Sezer, Familial Mediterranean fever: assessment of clinical manifestations, pregnancy, genetic mutational analyses, and disease severity in a national cohort, Rheumatol. Int. 40 (1) (2020) 29–40.

[37] L. Cantarini, G. Lopalco, C. Selmi, S. Napodano, G. De Rosa, F. Caso, L. Costa, F. Iannone, D. Rigante, Autoimmunity and autoinflammation as the yin and yang of idiopathic recurrent acute pericarditis, Autoimmun. Rev. 14 (2) (2015) 90–97.

[38] R. Siligato, G. Gembillo, V. Calabrese, G. Conti, D. Santoro, Amyloidosis and glomerular diseases in familial Mediterranean fever, Medicina 57 (10) (2021) 1049.

[39] A. Tufan, H.J. Lachmann, Familial Mediterranean fever, from pathogenesis to treatment: a contemporary review, Turk. J. Med. Sci. 50 (Sl-2) (2020) 1591–1610.

[40] D. Rigante, New mosaic tiles in childhood hereditary autoinflammatory disorders, Immunol. Lett. 193 (2018) 67–76.

[41] I. Grattagliano, L. Bonfrate, V. Ruggiero, G. Scaccianoce, G. Palasciano, P. Portincasa, Novel therapeutics for the treatment of familial Mediterranean fever: from colchicine to biologics, Clin. Pharmacol. Ther. 95 (1) (2014) 89–97.

[42] N.M. Ter Haar, K.V. Annink, S.M. Al-Mayouf, G. Amaryan, J. Anton, K.S. Barron, S. M. Benseler, P.A. Brogan, L. Cantarini, M. Cattalini, A.V. Cochino, F. De Benedetti, F. Dedeoglu, A.A. De Jesus, O. Della Casa Alberighi, E. Demirkaya, P. Dolezalova, K.L. Durrant, G. Fabio, R. Gallizzi, R. Goldbach-Mansky, E. Hachulla, V. Hentgen, T. Herlin, M. Hofer, H.M. Hoffman, A. Insalaco, A.F. Jansson, T. Kallinich, I. Koné-Paut, A. Kozlova, J.B. Kuemmerle-Deschner, H.J. Lachmann, R.M. Laxer, A. Martini, S. Nielsen, I. Nikishina, A.K. Ombrello, S. Ozen, E. Papadopoulou-Alataki, P. Quartier, D. Rigante, R. Russo, A. Simon, M. Trachana, Y. Uziel, A. Ravelli, M. Gattorno, J. Frenkel, Development of the autoinflammatory disease damage index (ADDI), Ann. Rheum. Dis. 76 (5) (2017) 821–830.

[43] R. Bourguiba, M. Delplanque, C. Vinit, F. Ackermann, L. Savey, G. Grateau, V. Hentgen, S. Georgin-Lavialle, Clinical course of COVID-19 in a cohort of 342 familial Mediterranean fever patients with a long-term treatment by colchicine in a French endemic area, Ann. Rheum. Dis. 2 (2020) annrheumdis-2020-218707. Epub ahead of print. doi: 10.1136/annrheumdis-2020-218707.

[44] Z. Günendi, F.G. Yurdakul, H. Bodur, A.K. Cengiz, Ü. Uçar, H.F. Çay, N. Şen, Y. Keskin, G. Gürer, M.A. Melikoğlu, D. Altıntaş, H. Deveci, M. Baykul, K. Nas, R. Çevik, A.Y. Karahan, M. Toprak, S. Ketenci, M. Nayimoğlu, İ. Sezer, A.N. Demir, H. Ecesoy, M.T. Duruöz, O.V. Yurdakul, A.B. Sarıfakıoğlu, Ş. Ataman, The impact of COVID-19 on familial Mediterranean fever: a nationwide study, Rheumatol. Int. 41 (8) (2021) 1447–1455.

[45] F. Haslak, M. Yildiz, A. Adrovic, S. Sahin, O. Koker, A. Aliyeva, K. Barut, O. Kasapcopur, Management of childhood-onset autoinflammatory diseases during the COVID-19 pandemic, Rheumatol. Int. 40 (9) (2020) 1423–1431.

[46] S.C. Güven, A. Erden, Ö. Karakaş, B. Armağan, E. Usul, A. Omma, O. Küçükşahin, COVID-19 outcomes in patients with familial Mediterranean fever: a retrospective cohort study, Rheumatol. Int. 41 (4) (2021) 715–719.

[47] F. Kharouf, Y. Ishay, A. Kenig, M. Bitan, E. Ben-Chetrit, Incidence and course of COVID-19 hospitalizations among patients with familial Mediterranean fever, Rheumatology 60 (SI) (2021) SI85–SI89.

[48] J.C. Tardif, N. Bouabdallaoui, P.L. L'Allier, D. Gaudet, B. Shah, M.H. Pillinger, J. Lopez-Sendon, P. da Luz, L. Verret, S. Audet, J. Dupuis, A. Denault, M. Pelletier, P.A. Tessier, S. Samson, D. Fortin, J.D. Tardif, D. Busseuil, E. Goulet, C. Lacoste, A. Dubois, A.Y. Joshi, D.D. Waters, P. Hsue, N.E. Lepor, F. Lesage, N. Sainturet, E. Roy-Clavel, Z. Bassevitch, A. Orfanos, G. Stamatescu, J.C. Grégoire, L. Busque, C. Lavallée, P.O. Hétu, J.S. Paquette, S.G. Deftereos, S. Levesque, M. Cossette, A. Nozza, M. Chabot-Blanchet, M.P. Dubé, M.C. Guertin, G. Boivin, Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3 randomised double-blinded adaptive placebo-controlled multicentre trial. Lancet, Respir. Med. 9 (8) (2021) 924–932 (COLCORONA Investigators).

[49] S.G. Deftereos, G. Giannopoulos, D.A. Vrachatis, G.D. Siasos, S.G. Giotaki, P. Gargalianos, S. Metallidis, G. Sianos, S. Baltagiannis, P. Panagopoulos, K. Dolianitis, E. Randou, K. Syrigos, A. Kotanidou, N.G. Koulouris, H. Milionis, N. Sipsas, C. Gogos, G. Tsoukalas, C.D. Olympios, E. Tsagalou, I. Migdalis, S. Gerakari, C. Angelidis, D. Alexopoulos, P. Davlouros, G. Hahalis, I. Kanonidis, D. Katritsis, T. Kolettis, A.S. Manolis, L. Michalis, K.K. Naka, V.N. Pyrgakis, K. P. Toutouzas, F. Triposkiadis, K. Tsioufis, E. Vavouranakis, L. Martinèz-Dolz,

B. Reimers, G.G. Stefanini, M. Cleman, J. Goudevenos, S. Tsiodras, D. Tousoulis, E. Iliodromitis, R. Mehran, G. Dangas, C. Stefanadis, G.R.E.C.C.O.-19 investigators, Effect of colchicine vs standard care on cardiac and inflammatory biomarkers and clinical outcomes in patients hospitalized with Coronavirus disease 2019: the GRECCO-19 randomized clinical trial, JAMA Netw. Open 3 (6) (2020), e2013136.

[50] K. Nas, N. Eryilmaz, M.F. Geyik, A. Altaş, COVID-19 in patients with familial Mediterranean fever treated with colchicine: case-based review, Rheumatol. Int. 41 (4) (2021) 811–817.

[51] S. Kobak, COVID-19 infection in a patient with FMF: does colchicine have a protective effect, Ann. Rheum. Dis. Jun 5 (2020), https://doi.org/10.1136/annrheumdis-2020-217882.

[52] M.N. Elshafei, A. El-Bardissy, A. Khalil, M. Danjuma, M. Mubasher, I.Y. Abubeker, M.F.H. Mohamed, Colchicine use might be associated with lower mortality in COVID-19 patients: a meta-analysis, Eur. J. Clin. Investig. 51 (9) (2021), e13645.

[53] N. Principi, Why it is important to develop an effective and safe pediatric COVID-19 vaccine, Vaccines 9 (2021) 127.

[54] D. Peckham, M.F. McDermott, S. Savic, A. Mehta, COVID-19 meets cystic fibrosis: for better or worse? Genes Immun. 21 (2020) 260–262.

[55] C.J. Peet, C. Papadopoulou, B.R.M. Sombrito, M.R. Wood, H.J. Lachmann, COVID-19 and autoinflammatory diseases: prevalence and outcomes of infection and early experience of vaccination in patients on biologics, Rheumatol. Adv. Pract. 5 (2021) (rkab043).

[56] U.M. Geisen, D.K. Berner, F. Tran, M. Sümbül, L. Vullriede, M. Ciripoi, H.M. Reid, A. Schaffarzyk, A.C. Longardt, J. Franzenburg, P. Hoff, J.H. Schirmer, R. Zeuner, A. Friedrichs, A. Steinbach, C. Knies, R.D. Markewitz, P.J. Morrison, S. Gerdes, S. Schreiber, B.F. Hoyer, Immunogenicity and safety of anti-SARS-CoV-2 mRNA vaccines in patients with chronic inflammatory conditions and immunosuppressive therapy in a monocentric cohort, Ann. Rheum. Dis. 80 (2021) 1306–1311.

[57] E.D. Batu, S. Özen, Implications of COVID-19 in pediatric rheumatology, Rheumatol. Int. 40 (8) (2020) 1193–1213.

[58] S. Kavukçu, A. Soylu, Could MEFV mutation carriage status have a protective role for COVID-19 pandemic? Med. Hypotheses 144 (2020), 109889.

[59] P. Schaner, N. Richards, A. Wadhwa, I. Aksentijevich, D. Kastner, P. Tucker, D. Gumucio, Episodic evolution of pyrin in primates: human mutations recapitulate ancestral amino acid states, Nat. Genet. 27 (2001) 318–321.