Editorial introductions

Current Opinion in Rheumatology was launched in 1989. It is one of a successful series of review journals whose unique format is designed to provide a systematic and critical assessment of the literature as presented in the many primary journals. The field of Rheumatology is divided into 15 sections that are reviewed once a year. Each section is assigned a Section Editor, a leading authority in the area, who identifies the most important topics at that time. Here we are pleased to introduce the Journal's Section Editors for this issue.

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Updates on interferon in juvenile dermatomyositis: pathogenesis and therapy

Hanna Kim

Purpose of review
This review provides updates regarding the role of interferon (IFN) in juvenile dermatomyositis (JDM), including comparison to interferonopathies and therapeutic implications.

Recent findings
Transcriptomic and protein-based studies in different tissues and peripheral IFN-α assessment have demonstrated the importance of the dysregulated IFN pathway in JDM. Additional studies have validated IFN-regulated gene and protein expression correlation with disease activity in blood and muscle, with potential to predict flares. Type I and II IFN both are dysregulated in peripheral blood and muscle, with more type I IFN in skin. Muscle studies connects hypoxia to IFN production and IFN to vascular dysfunction and muscle atrophy. JDM overlaps with interferonopathy phenotype and IFN signature. There are multiple case reports and case series noting decreased IFN markers and clinical improvement in refractory JDM with Janus kinase (JAK) inhibitors.

Summary
Studies confirm IFN, particularly type I and II IFN, is an important part of JDM pathogenesis by the level of dysregulation and correlation with disease activity, as well as IFN recapitulating key JDM muscle pathology. Smaller studies indicate there may be differences by myositis-specific autoantibody group, but validation is needed. JAK inhibitors are a promising therapy as they can inhibit IFN signaling, but further study is needed regarding which patients will benefit, dosing, and safety monitoring.

Keywords
biomarker, interferon, interferonopathy, Janus kinase inhibitor, juvenile dermatomyositis, pathogenesis

INTRODUCTION

Juvenile dermatomyositis (JDM) is a rare systemic autoimmune disease with inflammation and vasculopathy [1,2]. Myositis-specific autoantibody (MSA) groups define clinical subtypes within JDM [2,3]. About two-thirds of patients have a polycyclic or chronic disease course with persistent disease, despite high dose corticosteroids and/or other immunomodulatory medications [2,4,5], indicating a need for better therapies. Although much work has been done regarding evaluating different aspects of disease pathogenesis, the etiology is not fully understood [1,2,6]. In JDM, broad transcriptomic analyses previously found an upregulation of interferon-stimulated or interferon-regulated genes (IRGs) [7,8]. In this review, we will discuss updates on the role of interferon (IFN) in JDM.

Interferon overview

IFNs are named for their ability to interfere with viral infection, with a key role in both innate and adaptive immunity [9,10]. There are three types of IFN defined by their receptors [9] (Table 1). Type I IFN, which includes IFN-α and IFN-β, are mainly expressed by innate immune cells. Type II IFN, IFN-γ, is induced by activated immune cells. Type III IFN, IFN-λ, is restricted in tissue distribution, predominant at epithelial surfaces, and not highly expressed in hematopoietic cells [9]. As IFNs are typically present only in trace levels in peripheral blood and assays were not able to reliably detect them until more recently, surrogate methods for IFN detection were developed including measurement of IRGs and interferon-related proteins such as IP-10 [1,11,12].

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KEY POINTS

- IFN signature has been demonstrated in JDM peripheral blood, muscle, and skin. IFN-regulated markers (gene score or proteins) correlate with disease activity in blood and muscle.
- In vitro muscle studies show hypoxia leads to IFN production and IFN leads to vascular dysfunction and muscle atrophy.
- JDM overlaps with phenotype and IFN signature of Mendelian interferonopathies.
- JAK inhibitor therapy seems promising in JDM with clinical improvement and decreased IFN markers, but more information is needed regarding which patients to treat, dosing, and safety monitoring.

Interferon signaling

Type I, II, and III IFNs are a subset of type II cytokines. When these cytokines bind their receptors, it activates intracellular signaling via the Janus kinase (JAK)/Signal Transducers and Activators of Transcription (STAT) pathway (Table 1) [9]. JAKs phosphorylate when activated, and then the STATs phosphorylate, dimerize, and then translocate to the nucleus. There, they bind directly to DNA and induce cytokine-specific gene transcription, in this case, IFN-response genes (i.e. IRGs) leading to IFN-related protein translation [9,13].

INTERFERON SIGNATURE IN JUVENILE DERMATOMYOSITIS AND CORRELATION WITH DISEASE

Interferon-regulated genes in juvenile dermatomyositis

Increased IRG expression (IFN signature) in JDM was identified as the most dysregulated pathway by microarray initially from muscle of 4 JDM patients in 2002 [7] and peripheral blood 2 JDM patients combined with adult DM patients in 2007 [8]. Subsequent transcriptomic studies including RNA-Seq have validated this in muscle [14▪▪,15,16] and peripheral blood (whole blood or PBMCs) [17–19]. Although an IFN signature had previously been shown in adult DM skin [20], this was only recently demonstrated in 6 lesional JDM skin biopsies versus 8 controls [21▪▪]. The majority of highly expressed genes in JDM skin were IRGs, including *CXCL10*, *CXCL9*, and *IFI44L* [21▪▪]. A recent study from 24 JDM muscle biopsies found expression of the IRG *ISG15* was increased versus controls, which correlated with strength assessments [16]. Meta-analysis of 6 muscle and 2 skin transcriptomic analyses from adult DM and JDM found striking similarity of type I and type II IFN pathway dysregulation [22▪]. The IFN pathway is thought to be important in JDM as it was the most dysregulated pathway amongst broad transcriptomic analysis from multiple studies from peripheral blood and key tissues.

This has been supported by correlation of peripheral IRG scores with disease activity by many studies [19,23,24▪▪], generally with moderate correlation to global disease activity and muscle disease activity [25], including from longitudinal studies [1,26]. From one cross-sectional study with about 50 prevalent JDM patients, multivariable analysis identified weakness by Manual Muscle Testing (MMT) and musculoskeletal symptoms to be the best predictors of an elevated IRG score [24▪▪].

Transcriptomic analysis from sorted peripheral B-cells from 9 pretreatment and 9 posttreatment JDM patients and 4 health controls identified that IFN was the most dysregulated pathway in JDM [27]. Further cell-type-specific analyses are needed to elucidate the key cell types involved in the production and/or response to IFN in JDM.

Interferon-related proteins in juvenile dermatomyositis

IFN-related proteins have also been associated with JDM. This includes serum chemokines such

Table 1. IFN signaling by type

IFN type	Specific IFNs	Receptor subunits	JAKs	STATs
Type I IFN	alpha (α), beta (β), epsilon (ε), kappa (κ), omega (ω)	IFNAR1 IFNAR2	TYK2 JAK1	STAT1-STAT2 heterodimer
Type II IFN	gamma (γ)	IFNGR1 IFNGR2	JAK2 JAK1	STAT1-STAT1 homodimer
Type III IFN	lambda (λ)	IL10R2 IFNLR1	TYK2 JAK1	STAT1-STAT2 heterodimer

IFN, interferon; JAK, Janus kinase; STAT, Signal Transducers and Activators of Transcription.
From left to right, when a type I, II, or III IFN binds its receptor, its respective Janus kinases (JAKs) activate by phosphorylation. That causes the respective Signal Transducers and Activators of Transcription (STATs) to phosphorylate and dimerize. This leads to interferon-stimulated gene transcription and subsequent protein translation [9].

as MCP-1 and CXCL10/IP-10 [8], immunohistochemistry (IHC) for IP-10 in muscle [28], and IHC for MxA, an antiviral IFN-response protein, in skin [21▪▪,29]. A UK-based study from around 100 MxA-stained JDM muscle biopsies, found MxA correlated with clinical strength measures (MMT-8 and/or Childhood Myositis Assessment Scale [CMAS]) [25,30▪]. Peripheral neopterin, an IFN-γ stimulated protein, had moderate correlation with muscle strength impairment [31], and longitudinal assessment found neopterin decreased with remission [32]. Several studies correlated IFN-related peripheral chemokines level with JDM disease activity [19,33], including longitudinally [26,34], most with moderate to strong correlation with global disease activity, muscle disease, and/or extramuscular disease activity. A few studies simultaneously assessed IRG score and peripheral IFN-related chemokines [19,26], sometimes noting higher correlation with the latter, particularly with global and extramuscular activity. This may indicate that the IFN-related proteins are not produced in the blood, but rather are circulating from a different tissue source of disease activity.

Two IFN-related proteins, galectin-9 and CXCL10/IP-10 [35], were validated as sensitive and specific peripheral biomarkers of disease activity based on CMAS, MMT-8, and physician global disease activity assessment versus remission [36] in 125 patients from three cohorts (The Netherlands, United Kingdom, Singapore) [37▪▪]. This study included longitudinal analysis finding rising or persistent elevation of galectin-9 and/or IP-10 prior to disease flare, even when creatine kinase, a standard clinical laboratory muscle enzyme monitored in JDM, was not elevated. In 59 patients from 3 cohorts (Chicago, The Netherlands, Singapore), high levels of both markers were associated with more intensification of therapy and longer duration of treatment prior to drug-free remission [38]. Peripheral galectin-9 and IP-10 are promising biomarkers for monitoring disease activity and helping guide therapy, including potential flare prediction.

Possible differences by myositis-specific autoantibody group

Given that MSA groups define clinical subgroups in JDM, and IFN-related biomarkers seem to correlate with disease activity, there is interest in further assessing the IFN signature by MSA group. In one study, the anti-TIF1 JDM patient subgroup ($n = 20$) had higher correlation of IRG-score with skin-related disease activity measures, though they did not have significantly higher skin disease activity [24▪▪]. Another study found anti-NXP2 muscle biopsies ($n = 19$) had higher MxA staining, with lower staining in anti-MDA5 muscle biopsies ($n = 12$), though it is unclear if these MSA-group differences relate to differences by MSA group in clinical strength measures (CMAS and MMT-8), which correlated with MxA staining [30▪]. Other studies in blood [38], skin [21▪▪], and muscle [16,39,40] have done exploratory analysis (with $n<5$ per group) by MSA group, which indicate there may be differences in IRGs or interferon-related proteins by MSA group. However, confidence in true differences is limited by the small numbers analyzed. Evaluation of the potential differential role of IFN or IRGs by MSA group should be studied with larger cohorts and with longitudinal analysis.

UPDATES IN TYPE I AND TYPE II INTERFERON IN JUVENILE DERMATOMYOSITIS

Peripheral interferon-α in juvenile dermatomyositis

In 2017, Rodero *et al.* developed an ultrasensitive single-molecule array (Simoa) digital ELISA was used to quantify plasma IFN-α. JDM patients ($n = 43$) were found to have significantly higher IFN-α levels (median 46 fm/mL) versus healthy controls ($n = 20$, median 1.6 fm/mL). The IFN-α levels were found to correlate with IRG scores [41]. JDM cultured PBMCs were found to spontaneously secrete significantly more IFN-α than control PBMCs [42]. Thus, IFN-α, is higher in JDM peripherally and spontaneous made by JDM PBMCs. Continuing to investigate the source of IFN production in JDM will provide insight into IFN's role in JDM pathogenesis.

Specificity of interferon-regulated genes in peripheral blood

IFN-stimulated genes or IRGs are generally defined as any gene induced during IFN response [43]. Genes regulated by type I and II IFN are mostly overlapping including *CXCL10*, but some seem to be more specific to one or the other [44]. Most publications focus on peripheral type I IFN dysregulation in JDM [17–19] and IFN-α has been found to be elevated peripherally [41] as described above. To elucidate the peripheral IRG score in JDM, a IFN-γ (type II IFN) ratio amongst the IRGs [45] found that JDM had a higher type II IFN ratio. This indicates that type II IFN has a role in the peripheral IRG score, in addition to type I IFN.

Specificity of interferon-regulated genes in juvenile dermatomyositis skin

In Turnier's recent study of JDM skin, the transcriptome was compared to control keratinocytes treated

with IFN-α or IFN-γ. They found that JDM skin biopsies showed upregulation of IRGs stimulated by IFN-α, with less upregulation of IRGs stimulated by IFN-γ, particularly compared to SLE skin [21▪▪]. Thus, type I IFN may have a more prominent role in JDM skin.

Specificity of interferon-regulated genes in juvenile dermatomyositis muscle

Thirty-nine JDM muscle biopsies were evaluated for type I (*IFI27, IFI44L, IFIT1, ISG15, RSAD2, SIGLEC2*) and type II IFN IRG scores (major histocompatibility complex or MHC class II transcription activator or *CIITA, CXCL9*). Both scores were elevated in untreated JDM muscle and correlated with endomysial inflammatory cells ($CD3^+$, $CD68^+$) and perifascicular atrophy (PFA). The type II IFN score decreased with glucocorticoid therapy and high type II IFN score was associated with longer duration of active disease. IFN-γ was found to colocalize with $CD3^+$ T cells in JDM muscle, whereas it was not present in healthy muscle. These studies indicate a role for both type I and type II IFN in JDM muscle, with type II IFN score associated with response to therapy [46].

UPDATES ON ROLE OF INTERFERON IN JUVENILE DERMATOMYOSITIS MUSCLE

Interferon and perifascicular atrophy

Early capillary depletion, and then PFA are characteristic findings on muscle biopsy in adult DM and JDM. With chronic disease, there is evidence of chronic ischemia with neoangiogenesis [47,48]. *RIG-I*, an IFN-regulated gene, is overexpressed in areas of PFA [49]. The 3′ untranslated region (UTR) of *RIG-I* has a hypoxia response element (HRE). With in vitro myotube and muscle cell culture studies under hypoxic conditions, *RIG-I* expression was induced and type I IFN (IFN-β) was produced. Also, hypoxia inducible factor-1α and RIG-I were overexpressed in adult DM muscle biopsies with PFA. This indicates that hypoxia leads to increased type I IFN production and IRG expression in muscle in DM [50].

Introduction of type I IFN in vitro on myotubes derived from human muscle induces myotube or muscle atrophy. Treatment of human endothelial cells with type I IFN in vitro disrupts normal vascular network formation. Both effects were blocked by addition of ruxolitinib, a JAK inhibitor, which blocks IFN signaling [51]. Thus, type I IFN seems to induce muscle atrophy and vascular disruption in DM.

Myogenic precursor cells (MPCs) derived from JDM muscle biopsies were shown to have an angiogenic signature as well as an IFN-signature. IHC from DM muscle biopsies versus controls found JDM had more MPCs ($CD56^+$ cells) expressing IFN-β and angiogenic markers such as CCL2. MPCs derived from healthy muscle treated with IFN-β recapitulate pro-angiogenic gene signature and function. This indicates the role of IFN in inducing angiogenesis in DM muscle [52].

The above studies indicate that hypoxia/ischemia induces IFN production in muscle and IFN induces angiogenic functions by MPCs [50,52], as well as muscle atrophy and endothelial vascular network disruption [51].

RECENT INSIGHTS FROM COMPARISON OF JUVENILE DERMATOMYOSITIS TO MENDELIAN INTERFERONOPATHIES

Although IFN is clearly important in JDM pathogenesis, the exact mechanisms remain unclear. One way to gain insight on its role is by direct comparison to Mendelian interferonopathies, which have genetic mutations driving pathogenesis with high IFN signature [53]. Not only do JDM and Mendelian interferonopathies (IFN-opathies) share an IFN signature, but there is some phenotypic overlap. Clinical features of JDM and IFN-opathy cohorts were recently descriptively compared [24▪▪]. For example, about 50% of patients with Chronic Atypical Neutrophilic Dermatoses with Lipodystrophy and Elevated Temperature (CANDLE) caused by proteasome mutations have some evidence of myositis, which was present in all JDM patients included. Features of vasculopathy including interstitial lung disease are common in SAVI (STING-associated Vasculopathy with onset during Infancy) and JDM [24▪▪].

The plasma IFN-α level in JDM ($n = 27$) was generally lower than that of Mendelian IFN-opathies ($n = 27$), but not statistically different [41]. IRG-score comparison of 57 prevalent JDM patients with Mendelian IFN-opathies (10 CANDLE and 7 SAVI patients) found that JDM scores were significantly lower. However, the highest quartile of JDM IRG scores was as high as the Mendelian IFN-opathies. Principal component analysis found greater overlap between JDM and SAVI IRG scores, particularly for the anti-MDA5 JDM subgroup. This indicates that type I IFN and IFN-signaling through STING may be more important in JDM [24▪▪].

POTENTIAL THERAPEUTICS IN JUVENILE DERMATOMYOSITIS TO TARGET INTERFERON DYSREGULATION

Interferon-opathy treatment with Janus kinase inhibition

CANDLE and SAVI (IFN-opathies) are severe systemic autoinflammatory diseases with prominent

Table 2. Janus kinase inhibitor use in JDM

Ruxolitinib (*n*)	Tofacitinib (*n*)	Baricitinib (*n*)	References
1			Aeshlimann *et al.* [59]
		1	Papadopoulou *et al.* [58]
	2		Sabbagh *et al.* [57]
	2		Sozeri *et al.* [62]
		4	Kim *et al.* [55▪▪]
18	7		Ding *et al.* [56▪▪]
	3		Yu *et al.* [61]
7		3	Voyer *et al.* [60▪]
1			Heinen *et al.* [63]

Reports of use of off-label Janus kinase (JAK) inhibitors in JDM are listed above chronologically with the number of patients on a given JAK inhibitor. Ruxolitinib and bariciitnib block JAK1 and JAK2. Tofacitinib blocks JAK1, JAK2, and JAK3.

IFN signatures, that often have symptoms refractory to multiple biologic and nonbiologic immunomodulatory medications [53]. Eighteen IFN-opathy patients were treated off-label with baricitinib, a JAK inhibitor, as part of a compassionate use program with the hypothesis that blocking the pathogenic IFN-signaling could be more clinically efficacious. These patients had significant decrease symptoms such as pain, fatigue, fever, and rash, with decrease of inflammatory markers. IFN-markers (IRG score, IP-10) and STAT-phosphorylation also decreased with treatment as a proof-of-concept [54].

Janus kinase inhibitors in juvenile dermatomyositis

There are several case reports and case series that generally note clinical improvement in JDM (total 49 patients, 48 refractory, 1 new-onset) with off-label use of JAKi (ruxolitinib $n=27$, tofacitinib $n=14$, baricitinib $n=8$), listed in Table 2, including improvement in skin rash and/or strength. Ruxolitinib, tofacitinib, and baricitinib can inhibit type I, II, and III IFN signaling and a decrease in IRG score, IFN-related proteins, and/or STAT-phosphorylation was seen on JAKi treatment [55▪▪,56▪▪,57–59, 60▪, 61–63]. This may indicate that JAKi may better target key pathologic IFN dysregulation than other currently used medications, resulting in better management of JDM symptoms.

One study ($n=10$) noted while IFN-α was elevated in all patients prior to JAKi, it normalized with JAKi treatment by month 6 for both responders ($n=5$) and nonresponders ($n=5$), and the level of IFN-α elevation did not predict response [60▪]. Although many of the studies commented on safety parameters with some noting herpes zoster or BK virus titer changes [55▪▪,56▪▪,57–59,60▪,61,63], only three studies did monitoring prospectively [55▪▪,56▪▪,61] and only one systematically reported adverse events [55▪▪]. Additionally, varied JAKi dosing has been used and only one study ($n=4$) included pharmacokinetics evaluation [55▪▪]. Thus, JAKi are an exciting option in JDM that may be more targeted and thus provide increased efficacy, but further systematic studies to evaluate who to treat and when, with what dosing, and how to monitor safety, would be beneficial.

CONCLUSION

Multiple studies of transcriptomic analysis in muscle, peripheral blood, and skin find the IFN pathway most dysregulated, with evidence of type I and type II IFN involvement. IRG and IFN-related proteins in peripheral blood and muscle correlate with disease activity, with recent broad validation of galectin-9 and IP-10 in peripheral blood as promising biomarkers with potential to predict disease flares better than standard clinical muscle enzymes. Research is still needed regarding the assessment of differences by MSA group in different tissues, as well as investigating the primary tissue or cellular source of IFN in JDM.

Given the prominent IFN dysregulation in JDM, targeting IFN with therapy is of interest. Mendelian IFN-opathies provided some insight for IFN involvement as well as demonstration of clinical efficacy with inhibition of IFN signaling with JAKi and decrease of IFN markers. There are increased reports of clinical efficacy with JAKi treatment in generally refractory JDM with inhibition of different types of IFN signaling and similar decrease in IFN markers. However, further study is needed to better determine which JDM patients and when during the disease course JAKi should be used, at which dose, and with what type of safety monitoring.

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Conflicts of interest

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Clinical features of multisystem inflammatory syndrome in children

Jordan E. Roberts and Lauren A. Henderson

Purpose of review
To review diagnosis, clinical characteristics and treatment of multisystem inflammatory syndrome in children (MIS-C) associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Recent findings
MIS-C emerged in spring 2020 as a hyperinflammatory syndrome following SARS-CoV-2 exposure in children. Despite growing awareness of MIS-C, diagnosis remains challenging due to the range of phenotypes and severity. Fever accompanied by shock, cardiac dysfunction, gastrointestinal symptoms, or mucocutaneous signs suggestive of Kawasaki disease, especially in the presence of known or suspected coronavirus disease 2019 exposure, should trigger consideration of MIS-C. However, clinical presentations are highly varied and may overlap with other infectious diseases. Clinicians must maintain a high index of suspicion for MIS-C and be aware that patients may develop coronary artery aneurysms and myocarditis even with few or no Kawasaki disease symptoms. More precise diagnostic criteria and specific biomarkers are needed to aid diagnosis. Intravenous immunoglobulin (IVIG) is first-line therapy, and steroids should be considered as initial adjunctive treatment for patients with severe manifestations or other risk factors. Prompt treatment is essential, as patients may worsen acutely, though overall prognosis is reassuring.

Summary
MIS-C associated with SARS-CoV-2 has varied clinical manifestations. Clinicians must be aware of the common presentation and potential for decompensation and cardiac sequalae to guide appropriate evaluation and treatment.

Keywords
COVID-19, Kawasaki, multisystem inflammatory syndrome in children (MIS-C), pediatric, SARS-COV2

INTRODUCTION

Multisystem inflammatory syndrome in children (MIS-C) is one of the most concerning manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children. Despite increasing awareness of MIS-C, diagnosis remains challenging due to the shared symptomatology with acute coronavirus disease 2019 (COVID-19) and other febrile illnesses of childhood coupled with the lack of specific biomarkers for MIS-C. Given the risk of cardiovascular sequalae and progression to multisystem organ involvement and death, prompt recognition and treatment of MIS-C is essential. In this review, we discuss the emergence, clinical manifestations, and treatment of MIS-C.

EMERGENCE OF MIS-C

During the first months of the COVID-19 pandemic, reports of SARS-CoV-2 infection in children were reassuring, with low infection rates and few severe cases [1]. However, in late April 2020, alarming reports came from the United Kingdom of children presenting with hyperinflammatory shock and features of Kawasaki disease suspected to be related to SARS-CoV-2 exposure. Eventually, this entity would become known as MIS-C [2,3▪]. In the first series describing this syndrome, five of eight children required mechanical ventilation, one developed a giant coronary aneurysm, and one died, highlighting the critical nature of MIS-C [3▪]. All patients had positive SARS-CoV-2 serologies. An early case series from northern Italy, a European epicenter of COVID-19, reported a 30-fold increase in Kawasaki disease cases during 2020 compared to the 5 years preceding the COVID-19 pandemic [4▪]. These

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KEY POINTS

- Reliably identifying MIS-C remains difficult given the wide spectrum of phenotypes found in affected patients and similarity between MIS-C and other childhood febrile conditions.
- Validated diagnostic criteria that can be used in the clinical setting are lacking and need to be developed.
- The relationship between pre-pandemic Kawasaki disease and MIS-C remains unclear and while there are similarities in clinical features, patient with MIS-C may develop coronary artery aneurysms and cardiac dysfunction with few or no mucocutaneous features of Kawasaki disease.
- While there are no prospective studies comparing treatment approaches in MIS-C, there is evidence to suggest that rapid initiation of IVIG and glucocorticoids is beneficial.
- Multisystem inflammatory syndrome associated with SARS-CoV-2 also occurs in adults (multisystem inflammatory syndrome in adults) and is likely underrecognized.

children also presented with severe disease, with unusually high rates of macrophage activation syndrome and Kawasaki disease shock syndrome compared to Kawasaki disease in the pre-pandemic era. A total of 80% of children in the Italian study were seropositive for SARS-CoV-2, strengthening the presumed association with prior COVID-19 infection.

Additional studies from Europe and New York followed, with similarly high rates of shock and SARS-CoV-2 antibody positivity [5,6▪,7]. As MIS-C gained recognition, subsequent reports characterized a spectrum of disease severity, ranging from fever and systemic inflammation to critical illness [8,9▪,10].

CASE DEFINITIONS

Despite growing recognition, MIS-C is difficult to define. The Royal College of Paediatrics, Centers for Disease Control (CDC) and World Health Organization criteria are presented in Table 1 [11–13]. These case definitions were developed to expedite reporting of MIS-C to local health authorities, and thus are intentionally broad. Further, all were developed based on early reports which overrepresent children with the most severe phenotypes, and therefore may miss milder MIS-C. They are not validated for clinical diagnostic purposes, and may capture other febrile diseases. Given the differences in case definitions, studies that utilize different inclusion criteria are not necessarily comparable.

EPIDEMIOLOGY

Cases of MIS-C peak 2–6 weeks after highest community incidence of SARS-CoV-2 infections. In

Table 1. Multisystem inflammatory syndrome in children case definitions

	Royal College of Paediatrics and Child Health[11]	Centers for Disease Control[12]	World Health Organization[13]
Fever	Persistent fever > 38.5°C	Fever > 38.0°C for ≥24 h, or report of subjective fever lasting ≥24 h	Fever > 3 days
Evidence of SARS-CoV2 infection or exposure	SARS-CoV-2 PCR testing may be positive or negative	Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms	Evidence of COVID-19 (RT-PCR, antigen test or serology positive), or likely contact with a person with COVID-19
Clinical features	Inflammation (neutrophilia, elevated CRP and lymphopenia) AND Evidence of single or multiorgan dysfunction (shock, cardiac, respiratory, renal, gastrointestinal, or neurological disorder) with additional features	Laboratory evidence of inflammation AND Multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological)	Elevated markers of inflammation AND Two of the following: Rash/ mucocutaneous signs; Hypotension or shock; Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities; Coagulopathy; Acute gastrointestinal problems
Alternative diagnoses	Exclusion of any other microbial cause	No alternative plausible diagnoses	No other obvious microbial cause of inflammation
Level of care	Not specified	Hospitalization required	Not specified

COVID-19, coronavirus disease 2019; CRP, C-reactive protein; PCR, polymerase chain reaction; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

series with data on MIS-C patients' antecedent SARS-CoV-2 infections, MIS-C occurred a median of 21–25 days following initial respiratory symptoms [6▪,9▪]. Male predominance is reported in a majority of studies. Most children are previously healthy, though asthma and obesity are common [6▪,9▪]. Though initially described as a pediatric syndrome, nearly identical clinical presentations are reported in adults in increasing numbers [14▪].

Despite high rates of SARS-CoV-2 infections in China early in the pandemic, very few cases of MIS-C have been reported in East Asia. A review of Kawasaki disease cases from Tokyo showed neither increase in the prevalence of Kawasaki disease after the start of the COVID-19 pandemic, nor in rates of myocardial dysfunction [15]. However, in recent months, MIS-C cases have been observed in multiple other regions around the world, including Iran, India, South Korea, South Africa, and Latin America [16–20]. The rarity of MIS-C in East Asia is not fully understood, with some theories suggesting that differences in the immunogenicity of SARS-CoV-2 variants or host-related factors may explain this observation.

RACIAL/ETHNIC DISPARITIES

As early as the first UK series, racial and ethnic disparities in the incidence of MIS-C have been apparent [3▪]. Subsequent reports consistently demonstrate disproportionate rates of MIS-C in Black and Hispanic children. In the USA, 63% of MIS-C cases reported by the CDC were in Black or Hispanic children [21]. In New York, Black and Hispanic children were hospitalized with both acute COVID-19 and MIS-C at higher rates than White and Asian children (Fig. 1) [22]. It is difficult to determine if there is an additional preponderance of MIS-C cases beyond the disproportionately elevated risk of acute COVID-19 in Black and Hispanic communities. A large series evaluating MIS-C and pediatric acute COVID-19 found that children with MIS-C were more likely to be Black compared to non-Hispanic White children [23▪]. The reason for this increased MIS-C risk in Black children is not fully understood. Access to care for acute COVID-19 among Black children may play a role, as the reported rate of COVID-19 hospitalizations, though elevated for Black adults, underestimates the even larger disparity in the number of COVID-19 cases treated at home [24,25]. This situation may be exacerbated by lack of testing in predominantly Black communities, which leads to inaccurate data on COVID-19 community prevalence [26]. Socioeconomic status has been shown to be associated with pediatric acute COVID-19 infection, suggesting that risk factors, such as parental occupation, public transportation use, and crowding may be mediators of these disparities [27].

CLINICAL CHARACTERISTICS OF MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

While fever is universal, other clinical features of MIS-C vary, with some children presenting in fulminant shock while others may fulfil incomplete or complete Kawasaki disease criteria. Per CDC criteria, hospitalization is required, and most children in early series were admitted to the intensive care unit for vasopressor or respiratory support. However, other studies have reported children with only fever and systemic inflammation without end-organ involvement, highlighting the broad spectrum of disease [8,10].

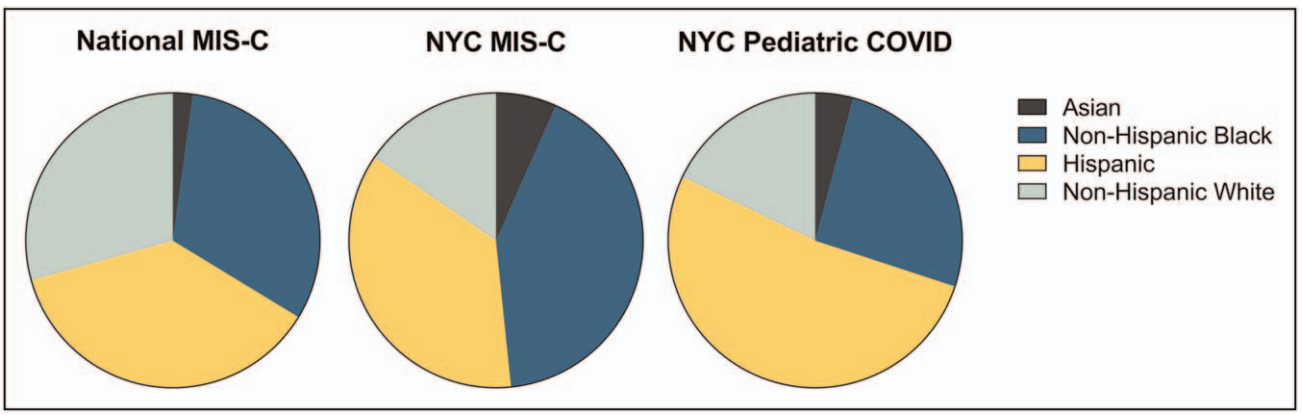

FIGURE 1. Racial and ethnic distribution of cases. *Data from Centers for Disease Control and Prevention. Health department-reported cases of multisystem inflammatory syndrome in children (MIS-C) in the United States, https://www.cdc.gov/mis-c/cases/index.html and Ref. [22].

CARDIAC

Myocarditis is one of the most alarming manifestations of MIS-C. While similar to Kawasaki disease shock syndrome, ventricular dysfunction occurs at higher rates in MIS-C, ranging from 34% to 62% in large series [6▪,8,9▪,10,28]. Patients frequently present with elevated markers of cardiac injury including troponin T, B-type natriuretic peptide (BNP), and N-terminal-proBNP [3▪,6▪,8,9▪,10]. Many require vasopressor support, including some children with normal ventricular function, suggesting vasodilatory shock. Reassuringly, most patients recover ventricular function during hospitalization [29,30], though some progress to profound myocardial dysfunction requiring extra corporal membrane oxygenation (ECMO) [7], and several children have died.

Coronary artery aneurysms (CAAs) or dilation are reported in variable proportions of patients within the acute period; large cohorts report CAAs (z score > 2.5) in around 13% [4▪,5,6▪,7,8,9▪,23▪]. Unlike myocarditis, CAAs do not appear correlated with degree of systemic inflammation [6▪]. Most aneurysms in series reporting dimensions are small, though large or giant aneurysms are also reported [3▪,6▪,8,28]. Some patients developed CAAs following the acute phase of illness, indicating a need for continued echocardiogram monitoring during convalescence [29,31]. While long-term data on CAAs in MIS-C are limited, one study reported resolution in over 90% of patients by 30 days [23▪].

Electrocardiogram (EKG) abnormalities and cardiac arrhythmias, particularly first-degree heart block, are reported in over half of MIS-C patients [30]. Rarely, progression to higher grade heart block is observed; one child had refractory arrythmias necessitating ECMO [3▪,32]. Illness severity appears to be associated with atrioventricular block; in one series, all patients with atrioventricular block were admitted to the intensive care unit (ICU) and had decreased ventricular function [30]. Monitoring EKGs in hospitalized patients every 48 h for development of arrhythmias is recommended [31]. Long-term cardiac sequalae of myocarditis remains an area of active concern and investigation, and patients require ongoing cardiology follow-up [29].

GASTROINTESTINAL

Gastrointestinal symptoms are reported in the majority of patients with MIS-C and may be the most common manifestation [9▪]. Most children have abdominal pain; diarrhea and vomiting are also common [6▪,8,28]. Abdominal pain is often severe and may be mistaken for acute appendicitis or testicular torsion [33–36]. In one report, a child with fever and right lower quadrant abdominal pain who underwent appendectomy subsequently developed shock with positive SARS-CoV-2 serologies. Pathology was atypical for acute bacterial appendicitis, with necrotizing lymphadenitis and vasculitis, suggesting MIS-C as the etiology [36]. Abdominal imaging may reveal ascites, adenopathy, and inflammation of the gallbladder or bowel; rarely, bowel wall thickening is profound enough to cause obstruction [6▪,33,34].

MUCOCUTANEOUS

Kawasaki disease-like mucocutaneous symptoms are described in multiple large cohorts, most commonly rash (52–63%), conjunctivitis (39–56%), oral mucosa changes (22–42%), and less often hand or foot swelling (9–37%), though some children have no Kawasaki disease features [6▪,8,9▪,23▪]. Large cervical lymph nodes appear less common (6–10%), though few series confirm node size [6▪,9▪]. Kawasaki disease-like presentations appear more common in younger children, and myocarditis is more prevalent in older children and teenagers [6▪]. Importantly, children with MIS-C who lack the mucocutaneous stigmata of Kawasaki disease have developed CAAs [8].

HEMATOLOGIC

Markedly elevated D-dimer levels are common in MIS-C and tend to be higher than in pediatric COVID-19 [37]. Due to the risk of thrombosis in adults with acute COVID-19, there is concern that coagulation abnormalities may confer increased clot risk in MIS-C. While one large series reported deep vein thrombosis or pulmonary embolism in 7% of adolescent patients with MIS-C [9▪], other studies report lower rates, including one meta-analysis demonstrating deep vein thrombosis or pulmonary embolus in only 3.5% of patients [38]. It remains unclear if there is an increased risk of thrombosis in MIS-C compared to other pediatric conditions that require intensive care, immobilization, and central venous access. One study showed schistocytes on peripheral blood smear in all MIS-C patients and elevated soluble sC5b-9, suggesting complement activation leading to microangiopathy [39]. This study also showed evidence of endothelial dysfunction in mild acute COVID-19, indicating that this may be a feature of SARS-CoV-2 infection, and not specific to MIS-C.

NEUROLOGIC

Headache is common, especially in adolescents. Altered mental status, encephalopathy, weakness,

and areflexia are less frequently reported. In a series of 1695 children combining MIS-C and acute COVID, 12% were found to have life-threatening neurologic manifestations including encephalopathy, stroke, and acute cerebral edema; 0.6% died from these complications [40]. Meningismus is also reported, though few children underwent lumbar puncture; in these patients, aseptic meningitis was confirmed with sterile CSF pleocytosis, absent oligoclonal bands and negative SARS-CoV-2 PCR [41,42]. Four children with new neurologic symptoms had magnetic resonance imaging signal abnormalities in the corpus collosum; all recovered [42]. Most strokes in MIS-C occurred in patients with other risk factors such as ECMO, bacterial co-infections (Lemierre, mastoiditis), or predisposing conditions (sickle cell). However, strokes are also reported in a small number of previously healthy children [40,43,44].

OTHER ORGAN SYSTEMS

The largest MIS-C series to date reports lower respiratory tract involvement in over 40% of patients [23▪]. A total of 52% of patients with MIS-C were PCR positive, higher than many studies, which may suggest that patients with acute COVID-19 were included in the MIS-C group. Series with lower PCR positivity have reported a relative lack of pulmonary involvement [3▪,4▪,5,6▪,8,9▪,23▪]. The cause of respiratory symptoms in MIS-C may be multifactorial and due to lingering effects of acute COVID-19 pneumonia, direct lung involvement from MIS-C, or from therapies such as fluid resuscitation. Less common symptoms of MIS-C include acute kidney injury, pancreatitis, and arthritis and arthralgia [9▪,45,46].

DIFFERENTIAL DIAGNOSIS

Clinical features of MIS-C are observed in many other childhood febrile illnesses, making the diagnosis of MIS-C challenging, and it is essential to rule out other infectious and oncologic causes. Empiric treatment for MIS-C while other studies are pending is often necessary in critically ill children. However, clinicians must be vigilant in considering other causes of fever, even in the setting of positive SARS-CoV-2 serologies or PCR, as children initially thought to have features consistent with MIS-C were later found to bacterial or viral infections, notably toxic shock syndrome and bacterial enteritis [47,48].

LAB FINDINGS

Systemic inflammation is required by all case definitions of MIS-C and found in essentially all reported cases in the literature. Laboratory features include elevated C-reactive protein, procalcitonin, ferritin, D-dimer, lactate dehydrogenase, fibrinogen and liver function tests [6▪,8,9▪]. Neutrophilia with accompanying lymphopenia and thrombocytopenia is common [3▪,4▪,5,6▪,7,8,9▪,10,23▪]. The majority (80–100%) of patients are SARS-CoV-2 antibody positive [4▪,5,6▪,8,9▪]. Fewer children (20–39%) have positive nasopharyngeal PCR testing, but cycle thresholds are higher in MIS-C than in acute COVID-19, indicating the detected virus may not be replicating [4▪,6▪,8,9▪,49].

TREATMENT

Children with MIS-C require multidisciplinary care from providers with expertise in rheumatology, cardiology, hematology and infectious disease. Given the multiorgan involvement of MIS-C, other subspecialists may be needed, and severely ill children will require admission to intensive care units. In this section, the focus will be on immunomodulatory treatment and anticoagulant use in MIS-C.

As MIS-C emerged, initial treatments were based on the similarity of MIS-C to Kawasaki disease and toxic shock syndrome. Intravenous immunoglobulin (IVIG) is used to prevent CAAs in Kawasaki disease and for immunomodulation in toxic shock [50]. Similarly, glucocorticoids are used in Kawasaki disease shock and refractory Kawasaki disease [51]. Glucocorticoids and IVIG are used in myocarditis, though evidence for these is mixed. By summer 2020, the RECOVERY trial demonstrated benefit of dexamethasone in patients hospitalized acute COVID-19, increasing clinician comfort with this approach [52].

IVIG and glucocorticoids remain the most common treatments for MIS-C, with a recent multicenter report indicating that 77% of patients with MIS-C received IVIG and 69% were treated with systemic steroids [23▪]. Similarly, a survey of physicians treating MIS-C reported that IVIG was the most common immunomodulator, though glucocorticoids were preferred for those with severe presentations or IVIG nonresponders, and anakinra (58%), infliximab (28%) and tocilizumab (8%) were also used [53].

Consensus treatment guidelines from the American College of Rheumatology (ACR) and the paediatric multisystem inflammatory syndrome temporally associated with COVID-19 National Consensus Management Study Group (UK) are presented in Table 2 [30,54▪,55▪]. Both the ACR and UK guidelines recommend IVIG at a dose of 2 gm/kg as first-line treatment; however, ACR advises against the use of a second dose of IVIG for refractory disease. Adjunctive first-line glucocorticoids are recommended by ACR in patients with organ-threating

Table 2. Treatment guidelines

	American College of Rheumatology (USA)[55]	**PIMS-TS National Consensus Management Study Group (UK)[54]**	
Date published	June 2020, Revised November 2020	September 2020	
Population applied to	Children with MIS-C	Children with PIMS-TS and Kawasaki disease-like phenotype	Children with PIMS-TS and nonspecific phenotype[a]
IVIG	2 g/kg based on ideal body weight First-line therapy in hospitalized MIS-C patients Second dose of IVIG not recommended	2 g/kg dosed on ideal body weight First-line therapy in all PIMS-TS with KD-like phenotype and in all treated nonspecific PIMS-TS patients Second dose considered for children who have not responded to the first dose	
Glucocorticoids	IV methylprednisolone (1–2 mg/kg/day) First-line *with IVIG* if shock or organ threatening disease *Second-line* in refractory disease in other children IV methylprednisolone (10–30 mg/kg/day) For treatment intensification in refractory disease 2–3 week steroid taper to prevent rebound	IV methylprednisolone (10–30 mg/kg/day) *First-line with IVIG* if < 12 months or coronary artery abnormalities *As second-line* in other children	IV methylprednisolone (10–30 mg/kg/day) *Second-line* therapy
Additional immunomodulation	High-dose anakinra if refractory to IVIG and/or steroids	Infliximab if nonresponsive to IVIG and steroids	Third line if nonresponsive to IVIG and steroids Consensus not reached; equipoise for tocilizumab, anakinra, and infliximab
Anticoagulation	Low dose ASA in all MIS-C patients without significant bleeding risk until normalization of plt count and confirmed normal coronary arteries. Anticoagulation if CAA with z-score≥10, documented thrombosis, or Or EF < 35%	If > 12 years, should wear compression stockings Low-dose ASA for minimum 6 weeks in all patients Local protocol for management of a thrombotic event Consult with hematologist re: long-term antiplatelet and anticoagulation therapy if CAA	
		Local protocol for KD ASA dosing	
Antimicrobial	Not addressed	If SARS-CoV-2 positive (RT-PCR or antigen), consider remdesivir IV antibiotics in all patients; should be focused or stopped on the basis of the clinical picture and culture results If criteria for toxic shock syndrome met, clindamycin in addition to broad-spectrum antibiotics	

[a]Treatment for this group is recommended in patients who have a coronary abnormality, TSS, progressive disease, or fever > 5 days. ASA, aspirin; CAA, coronary artery aneurysm; EF, ejection fraction; IVIG, intravenous immunoglobulin; IV, intravenous; MIS-C, multisystem inflammatory syndrome in children; PIMS-TS, paediatric multisystem inflammatory syndrome temporally associated with COVID-19; KD, Kawasaki disease; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TSS, toxic shock syndrome.

disease, whereas their use is limited to children under 12 months of age or those with CAAs by UK guidelines.

At the time of this review, no randomized trials exist to guide clinicians on the most effective MIS-C therapies. One study used propensity scoring to retrospectively compare initial treatment with IVIG alone versus IVIG plus methylprednisolone (1.6–2 mg/kg/day in most) and concluded that in addition to lower rates of treatment failure (defined as persistent or recurrent fever), those treated with glucocorticoids had reduced duration of ICU admission, need for hemodynamic support, and less ventricular dysfunction [56▪]. Steroids as adjunctive therapy also showed benefit over IVIG alone in one observational study measuring time to cardiac recovery [57]. At one center, instituting a clinical pathway which led to faster IVIG and glucocorticoid administration was shown to reduce overall and ICU length of stay [58]. In total, these studies suggest a benefit for rapid initiation of treatment and adjunctive steroids as part of first-line treatment in MIS-C.

One of the most pressing clinical questions is the need for anticoagulation in children with MIS-C. As discussed above, although D-dimers are markedly elevated in MIS-C, the true risk for thrombosis in these patients remains uncertain. Based on experience with Kawasaki disease, there is broad agreement that low dose aspirin should be provided to MIS-C patients without significant bleeding risk [50]. Similarly, there is general consensus that anticoagulants should be used in patients with severely decreased ejection fraction, large or giant CAAs, or evidence of clot, as aligned with prior clinical practice [30,54▪,55▪]. Clinicians should consider prophylactic anticoagulation as would be indicated for degree of critical illness, immobility, and glucocorticoid use. Due to the lack of evidence for universal anticoagulation beyond these indications, treatment based on laboratory evidence of hypercoagulability should be individualized according to patient risk factors. This topic remains controversial, and some guidelines suggest more aggressive anticoagulation based on D-dimer levels, including prophylaxis for all children with D-dimer > 5 times the upper limit of normal [59].

CONTROVERSIES AND QUESTIONS

Many controversies and questions remain in the diagnosis and treatment of MIS-C. Since its emergence, MIS-C and Kawasaki disease have been compared; however, the relationship between these two syndromes remains unclear. Possibilities include that MIS-C is a particularly severe variant of Kawasaki disease, a subset of MIS-C patients have Kawasaki disease, or the two entities should be considered as different etiologies entirely. Age appears to impact the presentation of MIS-C with higher rates of young children meeting Kawasaki disease clinical criteria, whereas adolescents more frequently present with myocarditis [6▪,60]. Thus, future studies may need to stratify patients by age. While the relationship between these diseases has yet to be fully elucidated, clinicians must approach management decisions with a clear understanding of the differences between MIS-C and pre-pandemic Kawasaki disease. MIS-C patients are at much greater risk of rapid decompensation and developing shock. Further, CAAs have occurred in MIS-C patients who have not met Kawasaki disease clinical criteria. Relatedly, multisystem inflammatory syndrome in adults (MIS-A) is increasingly reported, yet likely remains underrecognized, as older patients have fewer characteristic mucocutaneous features [14▪]. Clinicians must maintain a high degree of suspicion for this entity in teenagers and young adults who present with unexplained fever, particularly in the presence of confirmed or suspected COVID-19 exposure in the prior 1–2 months.

CONCLUSION

Despite advances in our understanding of MIS-C, this disease remains a diagnostic challenge due to the broad range of phenotypes and severity. Fever accompanied by shock, cardiac dysfunction, abdominal pain, or mucocutaneous signs in the presence of known or suspected COVID-19 exposure should trigger prompt evaluation. However, clinicians must be aware that patients may develop severe cardiac and other sequalae even with few or no Kawasaki disease symptoms. More precise diagnostic criteria and specific biomarkers are needed to aid diagnosis, especially as SARS-COV-2 antibody prevalence increases. Prompt treatment is essential, as patients may worsen acutely, though overall prognosis is reassuring. IVIG is first-line therapy, and steroids should be considered as initial adjunctive treatment, especially for patients with severe manifestations or other risk factors. Optimal anticoagulation remains controversial. Multidisciplinary involvement is essential to quality clinical care, and to optimize diagnostic and therapeutic approaches as new data emerge.

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Conflicts of interest

There are no conflicts of interest.

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Haematopoietic stem cell transplantation in paediatric rheumatic disease

Mario Abinun[a] *and Mary A. Slatter*[b]

Purpose of review
A small proportion of children affected by rheumatic diseases suffer from severe, progressive disease, resistant to conventional antirheumatic therapies and to biologic agents interfering with inflammatory cytokines, costimulatory molecules expressed on immune system cells and intracellular signalling pathways. Adding to the poor prognosis is a high risk from significant morbidity and mortality associated with long-term treatment with multiple, often combined anti-inflammatory and immunosuppressive agents. Carefully selected patients from this unfortunate group may benefit from treatment with haematopoietic stem cell transplantation.

Recent findings
The majority of patients with severe paediatric rheumatic and autoinflammatory diseases treated with autologous and/or allogeneic haematopoietic stem cell transplantation achieved long-term remission. However, the incidence of disease relapse and transplant related morbidity and mortality is still significant.

Summary
Careful patient and donor selection, timing of the transplant earlier in the course of disease rather than the 'last resort' and choosing the most suitable conditioning regimen for each individual patient are the major factors favouring successful outcome. Close co-operation between the patients, their family, and involved medical teams is essential.

Keywords
auto-inflammatory diseases, complete remission, disease relapse, haematopoietic stem cell transplantation, paediatric rheumatic diseases, transplant-related mortality

INTRODUCTION

Rheuma, from Greek: flowing current, a flux

The spectrum of paediatric rheumatic diseases – an umbrella term encompassing the musculoskeletal, arthritic, and connective tissue disorders with onset in childhood – includes newly defined diseases of immune dysregulation such as monogenic autoimmune and auto-inflammatory disorders [1▪▪,2▪]. Clinical features of many of these emerging inborn errors of immunity (IEI) overlap with those of 'classical' rheumatic diseases (Box 1), underlying the self-perpetuating activation loop of both innate and adaptive immunity as the main pathogenic mechanism [3,4▪,5▪]. Despite the 'treating to target' strategy and precision therapy for children affected by rheumatic disorders, even today a substantial percentage still has ongoing active disease into adulthood [6▪▪,7,8,9]. The prognosis is especially unfavourable for patients treated with multiple, combined immunosuppressive and anti-inflammatory agents (e.g., systemic corticosteroids, methotrexate, cyclophosphamide, cyclosporine, mycophenolate mofetil and variety of biologics) for a prolonged period (years, even decades) which significantly increases their risks from severe, life-threatening infections (Box 2) [10,11▪▪]. For such children, the only treatment option is haematopoietic stem cell transplantation (HSCT), often referred to as the 'last resort' or 'salvage' therapy [12,13].

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KEY POINTS

- Both autologous and allogeneic haematopoietic stem cell transplantation (HSCT) can induce complete, drug-free remission in patients with paediatric rheumatic diseases.
- Careful patient selection and the timing of HSCT, not as 'treatment of last resort' but earlier in the disease course, as well as choosing the most appropriate conditioning regimen are essential for reducing high transplant-related morbidity and mortality.
- The risks and benefits of HSCT should be carefully considered between the patient, parents, and the involved rheumatology and accredited transplant teams.
- If possible and applicable, every patient should be enrolled in a prospective trial, including immune monitoring and biobanking of clinical samples.
- Publication of experience, including single patient reports, is strongly supported.

Autologous (auto)-HSCT is a procedure where patient's own HSC are re-infused following an aggressive immunosuppressive (IS) conditioning regimen, often including ex-vivo T cell depletion (TCD) with the aim of removing auto aggressive lymphocyte clones, relying on the hypothesis that the newly developing immune system will re-establish immune tolerance [14,15]. Allogeneic (allo)-HSCT is the only cure for many IEI where the patient's faulty immune system is replaced with a graft from a healthy donor following myeloablative (MAC) or preferably reduced-intensity conditioning (RIC) regimens [1▪▪,2▪,16▪▪]. RIC leads to engraftment often with mixed donor chimerism, with a potential of inducing tolerance to allo- and auto-antigens and thus is favoured in the treatment of autoimmune diseases, whilst incurring the more limited nonhaematological toxicity associated with MAC [14,15,16▪▪]. Graft versus host disease (GvHD) prophylaxis is achieved with immunosuppressive drugs (calcineurin inhibitors, mycophenolate mofetil, methotrexate), serotherapy (anti T cell globulin, alemtuzumab) or rarely selective T cell depletion [17]. Transplant related mortality (TRM) of HSCT for severe autoimmune diseases is high; the unexpected 10–12% incidence reported for TCD auto-HSCT is due to profound and prolonged immunosuppression-related opportunistic infections [18,19], whilst GvHD is the main cause for ~20%

Box 1. Common overlapping clinical features of immune dysregulation disorders

- Systemic inflammation
  - fever
  - raised inflammatory markers (CRP, ESR, ferritin, etc.)
- Joint involvement
  - arthralgia
  - inflammatory arthropathy
- Skin involvement
  - vasculitis
  - vasculopathy
  - eczema
  - granulomas
  - blisters
  - panniculitis
- Lymphadenopathy
- Hepato- and splenomegaly
- Inflammatory bowel disease (IBD)
  - early onset severe enteropathy
  - colitis
- Interstitial lung disease (ILD)
- Organ specific autoimmunity
  - cytopenias
  - endocrinopathy

Box 2. Real-life example for '11 years of misery' (2011) (female, 12 years, at assessment for haematopoietic stem cell transplantation)

Systemic onset juvenile idiopathic arthritis diagnosed in the first year of life

- progressive polyarthritis, erosive
- growth retardation
- osteoporosis (vertebral fractures)

Therapy at the time of referral

- maintenance daily prednisolone (5 mg) and weekly methotrexate (15 mg)
- B cell depletion (rituximab) considered as the next step

Failed treatments

- long-term systemic steroids, methotrexate, intra-articular steroids
- blocking tumour necrosis factor-alpha (TNF) function (etanercept, infliximab)
- blocking interleukin-1 (IL-1) function (anakinra)
- blocking interleukin-6 (IL-6) function (tocilizumab)
- blocking T cell co-stimulation (abatacept)

Major issues

- progressive, active disease
- multiple complications
- multiple treatment failures
- extremely poor quality of life (QOL)

incidence for allo-HSCT [14,15]. Other downsides are the high rate of disease relapse even after years of stable remission, suggestive of only transient benefit of the auto-HSCT [18,19] and, surprisingly reported despite full donor haematopoietic engraftment for the allo-HSCT [20]. Development of secondary autoimmune diseases and occasional malignancies post-HSCT are potentially significant late effects [21].

In this review, we analyse the outcome of auto- and allo-HSCT for paediatric rheumatic diseases and selective monogenic autoinflammatory disorders presenting with 'rheumatic' phenotype.

HAEMATOPOIETIC STEM CELL TRANSPLANTATION

Autologous haematopoietic stem cell transplantation

The European Group for Blood and Marrow Transplantation (EBMT) Autoimmune Diseases Working Party (ADWP) database has over 3000 registered adult and paediatric patients from trials of auto-HSCT in rheumatoid arthritis, systemic lupus erythematosus (SLE), systemic sclerosis (SSc), Crohn's disease (CD), multiple sclerosis, and juvenile idiopathic arthritis (JIA) [22▪▪].

Table 1 summarises the outcome of auto-HSCT for 87 patients with severe paediatric rheumatic diseases, including JIA ($n = 57$), jSLE ($n = 11$), juvenile dermatomyositis (JDM; $n = 8$), jSSc ($n = 8$), and childhood-onset vasculitides ($n = 3$). The initial guidelines from the pioneering trial of TCD auto-HSCT for JIA in the Netherlands defined inclusion and exclusion criteria, immunosuppressive conditioning regimens and TCD methods, and these have been updated over the years [23–27]. Most patients benefited from the treatment. The initial phase of a two-step process is the improvement of acute inflammation early post-HSCT, a direct result of an immunosuppressive conditioning regimen. In the longer term, improvement in the quality of life (QOL) and the 'catch-up' growth were significant, although the established tissue and organ damage sustained pretransplant were not reversible. For the JIA cohort, a complete, drug-free remission (CR) lasting up to 20 years was achieved by 55% (31/57), partial remission (PR) by a further 11% (6/57), but disease relapsed in 23% (13/57), including in two patients after 7 and 9 years of CR indicating

Table 1. Autologous T cell depleted HSCT for paediatric rheumatic diseases

Disease No. of patients	Cond. regimen	Major complications	Outcome	Follow up	Reference
JIA (57) So-JIA ~80% Poly-JIA ~20%	IS	MAS Viral reactivation	31 CR 6 PR 13 Rel (2 D) *7 D	Up to 20 years	[18,19,28–42], (#)
jSLE (11) (^)	IS / RIC	MAS (splenectomy) Viral reactivation AI (AIHA, DM)	8 CR 3 Rel	9 months–7 years	[18,37,43–49], (^)
JDM (8)	IS/RIC	Viral reactivation	6 CR 2 PR (1 D)	8 months–7 years	[18,37,50–54]
jSSc (8)	IS	Rel. after 9 months CR (1) Disease progression (1)	4 CR 1PR 3 Rel	2–6 years	[5▪,55,56–58], ($)
Vasculitis (3) (PAN, WG, BD)	IS	AI (HT, AITP)	3 CR	9 months–2 years	[59–61]

Not all data regarding the conditioning regimens, infections, and outcome (remission, relapse, follow-up) are available. (^) jSLE – data for 17 patients from EMBT registry [49] and referred to in [18] are not included as not available. (*) JIA – treatment related mortality ($n = 9$ when including deaths of 2 patients following disease relapse).

Personal communications: (#) P. Veys and A. Lazareva (London), unpublished data for additional two patients with so-JIA transplanted in 2008 (m/5 years, Rel. 2-year post-HSCT) and 2010 (f/6 years, D 3 months post-HSCT from varicella-zoster virus pneumonitis and hepatitis associated with MAS), and long-term follow-up data; M Slatter (Newcastle), long-term follow-up data; ($) T. Cole and D. Hughes (Melbourne), unpublished data for an additional patient with jSSc (disease relapsed, proceeded to allo-HSCT).

Various immunosuppressive (IS) and reduced intensity conditioning (RIC) regimens: (IS): TBI/Cy/ATG; TBI/Cy; Cy; Cy/ATG (Alem); Flu/Cy/ATG; Flu/ALG. (RIC): Cy/ATG/Mel (Ara-c); BEAM; VP-16/TT.

AI, autoimmunity (post-HSCT); AIHA, autoimmune hemolytic anaemia; AITP, autoimmune thrombocytopenia; Alem, alemtuzumab; Ara-c, cytarabine; Ara-c, melphalan; ATG/ALG, anti-T lymphocyte globulin; BCNU, etposide; BD, Behcet disease; BEAM, carmustine; CR, complete, drug-free remission; Cy, cyclophosphamide; D, died; DM, diabetes mellitus; Flu, fludarabine; HT, hypothyroidism; MAS, macrophage activation syndrome; MAS, macrophage activation syndrome; Mel, melphalan; PAN, polyarteritis nodosa; PR, partial remission; Rel, relapse; TBI, total body irradiation; TRM, transplant related mortality; TT, thiotepa; VP16, etoposide; WG, Wegener granulomatosis/granulomatous polyarteritis.

the transient nature of the benefit at least for some patients, and seven patients died resulting in TRM of 12% (7/57) [18,19,28–42] (P. Veys, A. Lazareva, M. Slatter, personal communications). Of the 30 patients transplanted for other paediatric rheumatic diseases 70% (21/30) achieved long-term (up to 7 years) CR and further 10% PR, in 20% (6/30) disease relapsed, and one patient with JDM who achieved the only PR died [18,37,42–61] (P. Veys, T. Cole, D. Hughes, personal communication). Most of the patients who achieved PR, but only a minority of those in whom disease relapsed, responded well to subsequent medical treatment; others had a very poor prognosis with active and progressive disease. Profound and prolonged (6–12 months) immunosuppression caused by the conditioning regimen and TCD, but also by the pre-HSCT treatments, carries significant morbidity and mortality risks from frequent viral reactivation (herpes viruses, adenovirus, etc.), often associated with macrophage activation syndrome (MAS) [35,38,39,41,48,62–66].

Thymic reactivation, restoration of T-regulatory (T-reg) and naïve B cell networks, and of T-reg T cell receptor (TCR) diversity reported in patients who achieve CR, support the hypothesis that auto-HSCT can achieve resetting of the adaptive immune system [67–72]. Nevertheless, auto-HSCT treatment for paediatric rheumatic diseases declined in the last decade, caused mainly due to the advances towards precision medicine and because of the high incidence of TRM and of disease relapse [5▪,6▪▪,7,8,22▪▪]. Re-emergence of interest in auto-HSCT may depend on the results of further careful analysis of immunological processes, such as the normalisation of pre-HSCT deranged pattern of plasma cytokine profile and Treg TCR diversity in patients with JIA and JDM who remain in CR post-HSCT but not in those who relapsed [3,22▪▪,42,53].

Allogeneic haematopoietic stem cell transplantation

In addition, the remission of autoimmunity following allo-HSCT documented both in experimental animal models and case reports of patients with haematological diseases and concurrent autoimmune disease [73], numerous IEI disorders with prominent autoimmune features are cured with allo-HSCT [1▪▪,2▪,16▪▪]. Initially fully myeloablative protocols shifted towards less toxic RIC regimens, often resulting in mixed hematopoietic engraftment that may be adding to the induction of tolerance by the postulated 'graft-versus-autoimmunity' effect [15,16▪▪,74,75]. Concerns about high TRM and risk from GvHD are the main reasons for a small number of adult patients with rheumatic diseases undergoing allo-HSCT, and only very few children have been reported [13,15,76–82]. However, two retrospective outcome analyses of allo-HSCT in 50 patients with severe autoimmune diseases, of which 16 with rheumatic diseases, reported surprisingly good results. The EBMT ADWP (1984–2007) reported 55% achieving CR and further 23% PR, and the UK registry (1997–2009) 65% overall (OS) and progression-free survivals (PFS) at 5 years, albeit with TRM in the range of 20–30% for both [83,84]. Another recent EBMT survey (1997–2014) of the long-term outcome of 128 patients, of which 30 with well defined rheumatic diseases included 13 children from the international trial of allo-HSCT for severe JIA [85,86], reported CR in 67%, relapse incidence of 20%, and TRM at 100 days of 12.7% [20].

Table 2(a) summarises the outcome of allo-HSCT for 28 patients with severe paediatric rheumatic diseases [13,76–82,85,86]. Of the 18 patients with JIA, 15 improved within the first year post-HSCT and 13 of 15 (86.6%) achieved remission, whilst disease relapsed within 6 months post-HSCT in one of the two patients with only partial improvement. At a medium follow up of 4.5 years, 9 of 17 eligible patients (53%) remain in CR with significant improvement of arthritis and QOL, but the disease relapsed in 6 of 17 (35%). Interestingly, in five patients disease relapse occurred later, 6 years after PR in one and in another four after 1.5–10 years of CR. One patient with a diagnosis of RF-negative polyarticular JIA who failed allo-HSCT was eventually diagnosed post-HSCT with camptodactyly, arthropathy, coxa vara, pericarditis (CACP) syndrome by whole-exome sequencing confirming homozygous *PRG4* mutation [87]. Three patients developed significant grade II–IV acute GvHD, one of whom died early posttransplant from invasive fungal infection. Another patient died 20 months posttransplant from sepsis following an orthopaedic elective procedure, while in CR but still on immunosuppressive treatment for chronic GvHD; this patient previously failed a TCD depleted auto-HSCT [39]. Two patients from this cohort of severe JIA transplanted as 'the last resort' treatment died, resulting in TRM of 11.7% [85,86] (P. Veys, A. Lazareva, M. Slatter, P. Sedlacek, S. Chandra, R. Marsh, personal communications). Reassuringly there were no deaths reported in a smaller cohort of 10 children transplanted for other paediatric rheumatic diseases at the 'salvage state'; long-term CR was achieved in six (60%), PR in three, and one disease relapse occurred with a graft loss [13,76–82] (M. Slatter, T. Cole, D. Hughes, personal communications). Details of unpublished patients are shown in Supplementary Table 3, http://links.lww.com/COR/A50.

Table 2. Allogeneic HSCT for paediatric rheumatic diseases

(a) Rheumatic diseases (*n* = 28)				
Disease **No. of patients**	**Donors/cell source** **Conditioning regimen**	**Major complications**	**Outcome** **Donor chimerism**	**Ref.**
JIA (18) so-JIA (*n* = 12) poly-JIA (*n* = 6)	MUD (12), MSD (5), MFD (1) PB (12), BM (6) IS / RIC	GvHD Viral reactivation AI (GBSy; cytopenia)	FU 1–10 years CR (9); Rel (6); D (2) Chimerism (see text)	[85,86], (#)
¡SLE (4)	MSD (3), MFD PB (2), BM (2) IS/RIC	GvHD Viral reactivation AI (eczema, +ATPO Ab)	FU 2.5–15 years CR (3) (+ANA/CM Ab in 2); PR (1) 100% donor (all)	[13,76,77], ($)
Vasculitis (5) BD (*n* = 2) WG OLSy / PV CoAID (Pann.)	MSD (3), MFD (+bone chips), mMUC BM (3), PB, CB IS/RIC	GvHD Viral reactivation Splenectomy (1) AI (thyrotoxicosis/HT)	FU 1.5–10 years CR (3) (15–25 and 100%) PR (2) (>97 and 70%)	[13,78–82], ($)
¡SSc (1)	MSD BM RIC	Prev. failed auto-HSCT Initially 98% donor => graft loss	FU 1.5 years R (28%)	^
(b) Autoinflammatory diseases (*n* = 55)				
Disease **No. of patients**	**Donors/cell source** **Conditioning regimen**	**Major complications**	**Outcome** **Donor chimerism**	**Ref.**
FMF (2)	MSD MAC	GvHD *Klebsiella sepsis*	FU 2 years CR (1)	[103,104]
DADA2 (19)	MUD (11), mMUD (3), MSD, HSD BM (10), PB (5) MAC (10), RIC (6)	GvHD (10); VOD (2) Viral reactivation (12) PRCA/graft slipping – HSC boost (2) Graft loss (1); failure (2) => second HSCT (3) AI (cytopenias)	FU 5 months–13 years CR (all) 100% (16) Normal ADA2 (8)	[107–118]
PAMI (Hc/Hz) (5)	mMFD (2), MUD (2), MSD PB (4), BM (1) RIC	Inflamm. Sy (? cGvHD) (1) MAS/graft loss – second HSCT (1) Viral reactivation	FU 1–4 years CR (all); 100% (4), mix (1) Normal Zn (5) and CP (2)	[119▪]
MKD (9)	MUD (3), MSD (3), HPD (3) BM (4), UCB (2), PB (3) MAC (6), RIC (3)	GvHD (3) E. Sy (2); TMA (2); PRES (2) Ascites, sepsis – D (1) Viral reactivation (4); EBV-PTLD (1) Graft loss – second HSCT (1) AI (TT/HT; AIHA; psoriasis)	FU 8 months–14 years CR (7); Rel (1); D (1) 100% (all) Decreased uMA (4)	[120▪,121–125,126▪▪], ($), (*)
C1q-deficiency SLE (6)	MSD (2), mMUD (2), MUD, MFD BM (4), PB MAC/RIC	GvHD; MOF – D (1) E. Sy (1) Viral reactivation; EBV-PTLD (2) Rel./second HSCT / Aspergillosis/D (1) (100% donor, normal CH50, C1q 0)	FU 5 months–6 years CR (4); PR (Rel.) (1); D (2) 100% (3), 45% (1) Normal C1q (3) and CH50 (4)	[128–130,131▪], (#), (‘‘)
SIFD (4)	MUD (2) BM MAC / RIC	GvHD Enterobacter sepsis; viral reactivation Pulmonary haemorrhage – D (1) AI (AIHA/ITP) (1)	FU 3–6 years CR (3); D (1) Retinitis post HSCT (1) 100%	[132–134], (#)

Table 2 (*Continued*)

(b) Autoinflammatory diseases ($n = 55$)				
Disease **No. of patients**	**Donors/cell source** **Conditioning regimen**	**Major complications**	**Outcome** **Donor chimerism**	**Ref.**
RIPK1 deficiency (4)	MUD (3), HPD (1) PB RIC	GvHD (1) MOF (died) (1)	FU 1–8 years CR (3); D (1) 100% (all)	[135,136▪]
PFIT (3)	mMUD (2), MSD PB, BM RIC	GvHD; VOD; TMA E. Sy (ascites, pericardial eff.) Viral reactivation AI (AIHA)	FU 1–7 years CR (3)	[137,138,139▪]
TRAP1 (2)	MUD PB RIC	GvHD Viral reactivation	FU 10–12 years CR (2) (100%)	[140]
Unclassified (1)	MSD BM RIC	GvHD Viral reactivation	FU 6 years CR (mixed, high donor)	(£)

N.B. Detailed reports of unpublished patients are given in Supplementary Table 3, http://links.lww.com/COR/A50.
Not all data regarding the conditioning regimens, infections, and outcome (remission, relapse, follow-up) are available.
Personal communications: (#) P. Veys and A. Lazareva (London), M. Slatter (Newcastle), P. Sedlacek (Prague), S. Chandra and R. Marsh (Cincinnati), follow-up of patients with JIA post-publication [86] and data for additional 2 JIA patients (so-JIA, CR at 11 months; RF-negative polyarthritis, failed to respond; unpublished); ($) M Slatter (Newcastle), follow up of patients with jSLE and CoAID [13], and MKD [122], and unpublished data for additional patients with jSLE (1), MKD (1), C1q-deficient SLE (2) and SIFD (1); (∗) B Neven (Paris), follow-up of a patient with MKD [120▪]; (') P. Arkwright (Manchester), follow-up of a patient with C1q-deficient SLE [130]; (^) T Cole and D Hughes (Melbourne), data for a patient with jSSc (unpublished); (£) A. Lazareva (London) and S.H. Lum (Newcastle), data for a patient with unclassified autoinflammatory disease (unpublished).
Various conditioning regimens: MAC regimens: Bu/Cy/ATG (Alem); Bu/Flu/Alem (ATG); TBI/Cy/Ara-C; Treo/Flu/ATG (+Eto)
Immunosuppressive (IS) regimens: Cy; Flu/Cy/Alem; very low-dose Cy (high cumulative Cy dose pre-HSCT); TBI/Flu (Cy).
RIC regimens: Flu/Mel (Treo) (TBI) (TT)/Alem (ATG); TT/Mel/Alem; Treo/Flu/TT/ATG (Alem)/Ritux (for CD3TCR-ab/CD19 depletion).
GvHD prophylaxis was usually with cyclosporine (or tacrolimus) and mycophenolate mofetil (or methotrexate).
AI, autoimmune; AIHA, autoimmune haemolytic anaemia; Alem, alemtuzumab; ANA, antinuclear antibodies; Ara-c, cytarabine; ATG, anti T-cell globulin; ATPO, anti-thyroid-peroxidase antibodies; BD, Behcet disease; BM, bone marrow; Bu, busulfan; CM Ab, centromere antibodies; CoAID, complex autoimmune disease (pann., arthritis, hepatitis, PV); CP, calprotectin; CR, complete remission; Cy, cyclophosphamide; D, death; E Sy, engraftment (inflammatory) syndrome; EBV, Epstein Barr virus; Eto, etoposide; Flu, fludarabine; FU, follow-up; GBSy, Guillain-Barre syndrome; GvHD, graft versus host disease; HSD/HPD, haplo-identical sibling/parental donor; HT, hypothyroidism; IS, immunosuppressive conditioning regimens; Mel, melphalan; MFD, matched family donor; mM, mismatched; MOF, multi organ failure; MSD, matched sibling donor; MUD, matched unrelated donor; OLSy, overlap syndrome; Pann, panniculitis; PB, peripheral blood; PLTD, posttransplantation lymphoproliferative disease; PR, partial remission; PRCA, pure red cell aplasia; PV, pulmonary vasculitis; R, relapse; RIC, reduced intensity conditioning regimens; Ritux, rituximab; TBI, total body irradiation; TMA, thrombotic microangiopathy; Treo, treosulfan; TT, thiotepa; TT, thyrotoxicosis; UCB, umbilical cord blood; UCD, umbilical cord donor; UD, unrelated donor; uMA, urinary mevalonic acid; VOD, veno occlusive disease; WG, (Wegener) granulomatous polyarteritis; Zn, zinc.

Detailed immunological assessment will hopefully resolve the intriguing and important question of the high incidence of disease relapse following allo-HSCT [88]. The level of donor haematopoietic engraftment (myeloid and/or T cells) does not always match the disease outcome [89]. Late disease relapse occurred in five of six patients from the JIA cohort despite near to or 100% donor chimerism, only one had mixed low donor (8% in myeloid, and 57% in T cells) [86] (P. Veys, A. Lazareva, M. Slatter, P. Sedlacek, personal communications). Contrary to this, one patient from the JIA cohort and another from the recent trial of allo-HSCT for CD using umbilical cord blood as HSC source and a RIC regimen remain in CR > 5 years despite the absence of donor haematopoietic engraftment [86,90▪▪]. These data question the need for donor haematopoietic engraftment which is often associated with the risk of GvHD [89,90▪▪]. Alternatively, as engraftment exclusively in the Treg cell compartment was sufficient to cure IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome, an IEI with severely impaired function of T-reg cells due to *FOXP3* mutation, this may also apply for autoimmune diseases [91–93]. The effect of nonhaematopoietic mesenchymal stromal cells (MSC) and the survival of posttransplant minimal residual autoimmune disease have also been suggested to play a role [79,80,89,90▪▪,94].

Allogeneic haematopoietic stem cell transplantation for autoinflammatory diseases

Rapidly changing classifications of autoinflammatory disorders, firstly defined in the late 1990s, include disorders with features of systemic inflammation, immune dysregulation, combined

immunodeficiency, or bone marrow failure [1▪▪,2▪,4▪,95,96▪,97▪▪]. Despite the advances of 'precision treatment', some of autoinflammatory disorders are less responsive to novel biologic therapies [98▪,99▪,100] and prolonged interfering with inflammatory and/or other physiological pathways could lead to potentially serious adverse effects including severe infections [11▪▪,101,102]. For such patients unresponsive to medical therapies and/or those presenting an exceptionally severe phenotype of monogenic disorders, allo-HSCT is the treatment of choice [4▪,16▪▪,99▪,100].

Table 2(b) summarises the outcome of 55 patients, including the first report of a cure of familial Mediterranean fever (FMF) in a patient who had allo-HSCT because of an associated malignancy [103]. However, concerns were raised about the indications for HSCT [104–106]. More recently, a cohort of 19 patients transplanted for deficiency of adenosine deaminase type 2 (DADA2) had an excellent outcome, with all patients alive followed for 1–13 years, and with remission of not only the haematological and immunological manifestations, but also vasculopathy [99▪,107–118]. All five patients with proline-serine-threonine phosphatase-interacting protein 1 (*PSTPIP1*)-associated myeloid-related proteinemia inflammatory (PAMI) previously known as hypecalprotecinemia/hyperzincemia (Hc/Hz) syndrome are alive, followed for 1–4 years and in CR [119▪]. Seven out of nine patients transplanted for mevalonate kinase deficiency (MKD) and followed from 1 to 14 years are in remission, one graft failure following a TCR-alpha/beta/B cell depleted transplant from haploidentical parental donor was rescued by second HSCT with a RIC protocol from the same donor, and one patient died from sepsis 3.5 months post-HSCT [120▪,121–125,126▪▪] (B. Neven, M. Slatter, personal communications]. In one patient relapse of autoinflammatory features at 18 months post-HSCT from unrelated umbilical cord donor with a MAC regimen coincided with the raising levels of urinary mevalonic acid, which was unmeasurable initially post-HSCT, despite 100% donor chimerism [126▪▪]. Four of the six patients transplanted for C1q-deficient SLE, recently classified as type I interferon-mediated monogenic autoinflammatory disorders [127], are in CR followed up to 6 years; however, two patients died, one from gut GvHD and multi-organ failure (MOF), another from disseminated aspergillus infection early post-second HSCT performed 3 years after the first HSCT because of the graft failure and disease relapse with CNS vasculitis [128–130,131▪] (P. Arkwright, M. Slatter, personal communications). Of the four patients transplanted for sideroblastic anaemia with immunodeficiency, fevers, and developmental delay (SIFD) due to *TRNT1* mutation(s), three are in remission followed from 3 to 6 years and one died from pulmonary haemorrhage [132–134] (M. Slatter, personal communications). Similarly, three out of four children transplanted for autoinflammation, arthritis, and very early onset inflammatory bowel disease (VEOIBD) due to RIPK1 deficiency are in remission followed from 1 to 8 years, but one died from MOF early posttransplant [135,136▪]. Outcome is good for another six children with rare disorders, including three with autoinflammatory periodic fever, immunodeficiency, thrombocytopenia (PFIT) due to *WDR1* mutations of which one with VEOIBD phenotype [137,138,139▪], two with autoinflammation due to mutations in *TRAP1* encoding a mitochondrial chaperone protein [140], and one with unidentified disorder, with resolution of inflammatory, immunological and IBD features (A. Lazareva, S.H. Lum, personal communications). Details of unpublished patients are shown in Supplementary Table 3, http://links.lww.com/COR/A50.

Both MAC and various RIC protocols achieved the essential myeloid engraftment resulting in normalisation of biomarkers when measured (e.g., ADA2, zinc, calprotectin and/or C1q blood levels, complement classical pathway function, urinary mevalonic acid), and long-lasting donor chimerism in the majority [99▪,119▪,120▪,131▪]. Six patients (11%) required second conditioned allo-HSCT because of the initial graft failure. Overall, 48 of 55 patients (87%) are in remission, disease relapse occurred in two of which one died following a second conditioned HSCT, and TRM was 9% (5/55). Serious complications included frequent viral reactivation, significant acute and chronic GvHD often associated with the severe inflammatory syndrome, transplant-related thrombotic microangiopathy (TMA), hepatic veno-occlusive disease (VOD) in patients from DADA2 cohort, and secondary autoimmunity post-HSCT [99▪,141,142–144]. Because of the ubiquitous nature of the action of a number of the mutated genes causing IEI [1▪▪,2▪], it is not expected from successful allo-HSCT to rescue all components of the immune dysregulation phenotype as outlined for VEOIBD features of RIPK1 deficiency [135,145]. However, recent results are encouraging [136▪] and especially favourable for patients with severe DADA2 [107,146] and PAMI [119▪]. Control of the inflammation pre-HSCT with judicial use of steroids and biologics to minimise the risk from GvHD and other serious complications is very important, as is the vigilant monitoring for or prophylaxis of VOD in the case of DADA2 [119▪,120▪,146].

CONCLUSION

According to the current guidelines auto-HSCT may be considered for carefully selected patients, whilst allo-HSCT is indicated for patients with monogenic autoinflammatory diseases with a severe phenotype and should be considered for other paediatric rheumatic diseases only as part of a carefully monitored clinical trial [26,27]. For the individual patient, the decision whether to proceed with auto- or allo-HSCT is best made after a careful consideration of the risks and benefits between the patient, parents, and involved rheumatology and transplant teams [22▪▪,147,148–150]. The overlap of clinical features may lead to misdiagnosis of a 'mimicking' disease not treatable by HSCT, and the nonhaematopoietic dependent features of the disease and/or the pre-HSCT established damage of organs and tissues cannot be rescued by HSCT [87,132,145,151▪▪]. Therefore, the results of critical immunological, cytokine profiling, and genotyping tests should ideally be available before the decision for HSCT is reached [152,153▪]. Experience is supporting use of RIC regimens, and preferring a healthy matched unrelated donor over family members and/or matched unrelated umbilical cord donors when the disease-causing gene mutation is unknown [16▪▪,17,154–155,156▪▪]. Other cell-based therapies such as mesenchymal stromal cells and gene editing and/or therapy for monogenic disorders are promising new breakthroughs [94,157,158]. Addressing the need for extended, prospective clinical trials of HSCT against biologic therapies, and the challenges of significant disease relapse rate and high transplant-related morbidity and mortality are likely to determine the future role of HSCT in the treatment of paediatric rheumatic diseases [22▪▪,159].

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Update in familial Mediterranean fever

Seza Ozen

Purpose of review
Familial Mediterranean fever (FMF) is the prototypic autoinflammatory disease. Although the gene associated with the disease was identified 24 years ago, we still have to learn about the pathogenesis of its inflammation and the variation in the phenotype. In this review, we discuss some recent findings in FMF, such as changes in our understanding of the genetics, aims to define new criteria, and factors contributing to the disease presentation.

Recent findings
We finally have learned why a mutation causing this disease was selected in ancient times; *MEFV* gene mutations confer resistance to the microbe of plague. A group of experts have outlined recommendations for the analysis of the genetics of FMF. These recommendations complement the new classification criteria, which includes genetic results. In the past year, a number of studies have addressed the contributing factors to the inflammation caused by the mutations in pyrin; this has included epigenetic studies as well. Finally, we have long-term data for the use of anti-IL1 treatment in colchicine-resistant patients.

Summary
We now have recommendations for assessing genetic analysis of the *MEFV* gene and how to reliably classify a patient as FMF. We await further data to understand the contributing genetic and environmental factors that affect the inflammation and final phenotype in FMF and the extent of the disease presentation.

Keywords
comorbidity, familial Mediterranean fever, heterozygote, *MEFV* mutations

INTRODUCTION

Familial Mediterranean fever (FMF) is the most common autoinflammatory disease and it has opened a new chapter in rheumatology. FMF is associated with mutations in the *MEFV* gene coding for the protein pyrin. Although it is the first autoinflammatory disease to be defined, FMF continues to challenge us. In this past year, we have gained important insight into a number of new data that may solve some of our problems with this disease.

BLESSING IN DISGUISE: THE CURIOUS CASE OF THE EFFECT OF ANCIENT FAMILIAL MEDITERRANEAN FEVER MUTATIONS ON RESISTANCE TO YERSINIA PESTIS

FMF is very common in the eastern Mediterranean where the carrier rate is as high as 1/6–1/10 [1▪]. We have long wondered why an error, which may even cause mortality with secondary amyloidosis in the homozygous state, was selected in the region and what evolutionary force drove this change.

Six years ago a scientist from a country where FMF is very rare, introduced a milestone concept for the activation of pyrin: they showed the Pyrin-mediated caspase 1 inflammasome activation in response to rho-glucosylation activity of *Clostridium difficile* [2]. They, therefore, suggested a new concept in our innate immune system where pyrin functions to sense pathogen modification and inactivation of Rho GTPases. This led to another groundbreaking article suggesting that the advantage of the carriers (and patients) was against *Yersinia pestis* [1▪] and the evolutionary pressure for selection was introduced by the microbe of the plague. The authors reach this conclusion through a sophisticated study in population genetics, and through analyzing the biology of pyrin and YopM, as well as historical records. The eastern Mediterranean was in the major crossroads between Asia and Europe in the dissemination of the

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KEY POINTS

- Carriers for MEFV mutations seem to have an advantage for an improved immune response against *Yersinia pestis*, the cause of plague.
- The presence of variants of unknown significance and other contributing factors complicate the interpretation of the genetic analysis for FMF.
- The new Eurofever/PRINTO endorsed classification criteria for FMF also includes the genetic analysis and has been validated in a multiethnic cohort.
- Anti-IL1 treatment is effective for FMF patients who are resistant to colchicine.

plague pandemic, and thus, would have been ideally located to select for FMF variants that are protective against *Yersina* [1▪]. Mutations in *MEFV* were not selected globally as they were only present at the appropriate time in that limited geographic distribution [1▪]. The readers are referred to the elegant figures especially those presenting representative trajectories from forward-time simulation of episodic selection and how this has affected disease-causing mutations in the gene (Fig. 1d of Park *et al.* [1▪]).

HOW SHOULD WE ASSESS THE RESULTS OF GENOTYPING, *QUO VADIS*?

Sanger sequencing is still the recommended initial molecular testing for FMF. This method is well suited for low-throughput laboratories for which a next generation sequencing approach would not be profitable [3,4▪]. A panel of experts have developed updated recommendations for the testing of the common autoinflammatory diseases including FMF. The expert panel met face to face after two surveys and included European Molecular Genetics Quality Network members and members of ISSAID with expertise in the relevant diseases [4▪]. For FMF, it is recommended to screen exon 10 mutations and p.(Leu110Pro), p.(Glu148Gln), p.(Pro369Ser), p.(Arg408Gln), p.(Ile591Thr) (Table 1).

As FMF is an autosomal recessive disease, the diagnosis is confirmed if there are two pathogenic mutations. However, if one single nucleotide polymorphism is a variant of unknown significance, then diagnosis depends on clinical judgment and criteria (ISSAID/EMQN). Parental testing is recommended to resolve the issue of complex allele (cis position). On the other hand, if there is only one pathogenic mutation or two variants of unknown significance this genotype is inconclusive; the diagnosis will again rely on clinical judgment and criteria [4▪]. One should remember that rare variants may exist if only a limited number of exons were screened. When the genotype is inconclusive, one should consider larger testing for the other autoinflammatory diseases as well (Fig. 1). The genetic testing is also complicated with the possible presence of digenic mutations in another *AID* gene and the rare dominant transmission as p.(Met694del) can sometimes cause an autosomal dominant disease.

In the aforementioned report, variants of unknown significance (VUS) are also defined in detail:

(1) VUS is the first report of a gene variant associated with a typical autoinflammatory phenotype but lacking familial segregation data; thus pathogenic role is not guaranteed [4▪].
(2) It is a rare/novel variant in a gene associated with recessive SAID, reported in a patient with multifactorial autoinflammatory syndrome (e.g. periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis) [4▪].
(3) VUS are frequent gene variants often found with various phenotypes atypical for the associated SAID and with incomplete familial segregation. Some show sub-pathogenic effect on a core pathogenic gene activity. These variants could be inflammatory or disease specific risk factors whose clinical expression depends on additional genetic/environmental factors; for example, p.(Glu148Gln) in the Mediterranean fever (*MEFV*) gene [4▪].

So we need good clinical criteria to define the disease, and to start treatment.

Table 1. Recommendations for screening and interpretation of variants in the *MEFV* gene

Pathogenic mutations in exon 10	Classical FMF
p.E148Q, p.L110P, p.P369S	Frequent VUS, often allelic (complex alleles)
p.P373L, p.H478Y, p.M694del, p.T577	Sometimes associated with dominant FMF-like transmission
p.P373L, p.H478Y, p.M694del, p.T577	Associated with dominant transmission (neutrophilic dermatosis)

Modified with permission from [4▪]. FMF, familial Mediterranean fever; VUS, variant of unknown significance.

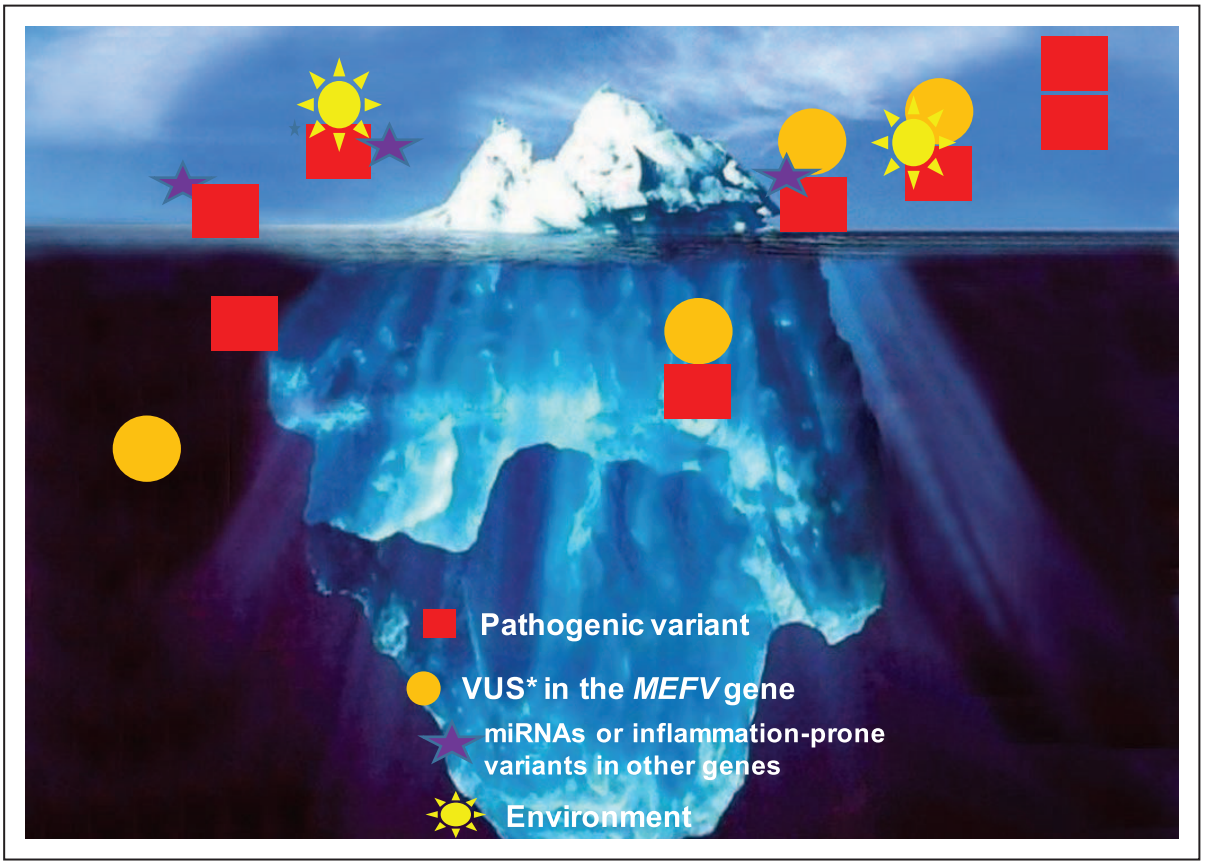

FIGURE 1. A patient with one mutation only (heterozygote) can display the familial Mediterranean fever (or familial Mediterranean fever-like phenotype if the other allele carries single nucleotide polymorphisms that would render the individual more inflammatory, and/or has a VUS (*variant of unknown significance) as well, or because of certain triggering environmental factors.

CRITERIA, CRITERIA...

There have been previous attempts to develop classification or diagnostic criteria for FMF. However, we now have classification criteria for the four common monogenic periodic fever diseases, including the genotype result as well. These criteria were developed with a panel of 25 clinicians and 8 geneticists going through multiple steps for the selection of the best candidate classification criteria with appropriate statistical analysis; the final step was the cross-sectional validation of the novel criteria [5]. According to this new Eurofever/PRINTO endorsed criteria, in a child with confirmatory genotype for FMF, only one of the criteria below is required to classify as FMF:

(1) Duration of episodes 1–3 days;
(2) Abdominal pain;
(3) Chest pain;
(4) Arthritis.

However, if the genotype is not confirmatory (see above), you need at least two of these criteria [5]. If the genotype is not confirmatory, the author suggests that a panel for the other common periodic fever diseases should also be done, especially if the child is not of eastern Mediterranean descent.

The performance of these criteria have already been tested in a couple of different centers. Tanatar *et al.* have compared the performance of the aforementioned criteria to the previous Tel Hashomer, Livneh and pediatric criteria. They concluded that the performances of all criteria were similar for homozygous and compound heterozygous patients. However, the new criteria did not perform so well in heterozygous patients [6].

Sag *et al.* also compared the existing criteria and concluded that the new Eurofever/PRINTO criteria had a better sensitivity but lower specificity compared with the other criteria. They suggested that the lower specificity in the Turkish cohort might have been because of high carrier rate in the population [7].

Another set of criteria addressed an unmet need: definition of colchicine resistance. The expert panel suggested definitions for both resistance and intolerance to colchicine through a series of Delphi exercises, following systematic literature review,

and a final consensus meeting [8]. This criteria defines colchicine resistance as: for a patient receiving the maximum tolerated dose of colchicine, ongoing disease activity by recurrent clinical attacks (average one or more attacks per month over a 3-month period), or persistently elevated C-reactive protein or serum amyloid A in between attacks, in the absence of any other plausible explanation. We believe these criteria are important for decision-making in the use of anti-IL1 treatment. We also believe this will guide the health authorities in defining the coverage of biologic treatment [8].

HOW DO YOU EXPRESS THE PHENOTYPE/THE DISEASE?

Patients with the FMF phenotype but with only one pathogenic mutation have been described both in areas where the disease is frequent as well as all around the world. We have long searched for answers to explain how an autosomal recessive disease could be expressed with one mutation only. A number of articles suggesting an explanation have emerged this year. Schnappauf *et al.* [3] have reported that heterozygous mutations in other domains of pyrin affect residues critical for inhibition or protein oligomerization, and lead to constitutively active inflammasome, and thus to a subclinical inflammatory phenotype in healthy carriers of FMF mutations. Indeed, we and others have shown that carriers for MEFV mutations displayed higher C-reactive protein levels and had more rheumatic or inflammatory diseases.

Umar *et al.* [9] have tried to understand how patients with one mutation expressed a disease, by using high-coverage whole genome screening. In a couple of their patients, they identified some variants in other autoinflammatory disease genes, which is the case in similar studies. They further investigated the presence of variants in other novel genes, including the exonic regions; one candidate was surprisingly in the type I interferon-signaling pathway. The second candidate gene was a variant in IL-1 receptor-like 1 gene and the deletion was present in nine FMF patients with a single mutation in the *MEFV* gene [9].

Akkaya-Ulum *et al.* [10] have investigated whether noncoding RNAs may have an effect in disease expression in FMF (mir197). In their FMF cohort, a number of functional assays including caspase activation suggested that a miRNA, mi-197-3p had an important role in the inflammation of these patients. They further showed through 3UTR luciferase activity assay that miR-197-3p binds to the IL-1beta receptor, *type I (IL1R1)* gene, which is critical in inflammation [10]. Karpuzoglu *et al.* [11] have also studied miRNAs in FMF and have shown deregulation in 26 apoptosis-related miRNAs in FMF (miR). They speculated that these miRNAs may be involved in FMF pathogenesis by affecting apoptotic pathways; however, they lacked functional studies, which prevents us from drawing conclusions.

Finally the effect of microbiota has been investigated in a study from Turkey and the United States. Fecal samples of patients were collected in FMF patients with severe and mild diseases as assessed by AIDAI. The authors failed to show any difference in microbiota among severe versus mild patients in any of the regions. However, there was a difference in the fecal microbiota composition between the two countries [12]. As in the United States cohort, there were patients with high AIDAI scores as well, the authors were not able to comment on the effect of the differences between the two countries. One limitation of the study was the low number of healthy controls. The oral microbiota or other environmental factors remain to be studied.

Thus, it is tempting to suggest that carrying a *MEFV* mutation be a significant risk factor for symptoms or the phenotype of 'FMF'; the allele without a pathogenic mutation may contribute in a multifactorial fashion, either carrying inflammation-prone variants in the innate immune pathway or through epigenetic changes and maybe by changes introduced with the environment. The effect of VUS in the other allele may also contribute in this fashion. One may think of the FMF 'phenotype' as the portion of the iceberg above surface (Fig. 1). The portion below water is waiting to display features with the contributory factors.

IT IS NOT JUST THE ATTACKS BUT COMORBIDITIES AS WELL

As we have understood that mutations in the *MEFV* gene increase the inflammatory response, it is not surprising that FMF patients have associated comorbidities. Balci-Peynircioglu *et al.* [13] have analyzed the comorbidities in 2000 FMF patients; they categorized comorbidities as those associated with FMF per se, such as secondary amyloidosis; those because of increased innate inflammation and those that were regarded as incidental. The results showed that ankylosing spondylitis (sacroiliitis), Behçet disease, IgA vasculitis (Henoch Schonlein purpura), juvenile idiopathic arthritis (JIA), polyarthritis nodosa and multiple sclerosis were increased inpatients with FMF [13]. The authors suggested that this was because of the increased innate immune response in carriers for the *MEFV* mutation. On the other hand, autoimmune diseases, such as systemic lupus erythematosus was not increased [13]. Watad *et al.*

[14] confirmed the high association of FMF with ankylosing spondylitis, Behçet disease and psoriasis; they hypothesized that the association with these MHC I-opathies suggested that the tissue-specific dysregulation of innate immunity shared between FMF and these disease may drive adaptive immune system-associated disorders [14]. However, this view does not explain the high rate of the other aforementioned diseases.

A study of 57 Chinese children with systemic onset JIA also confirmed that an exon 10 mutation in *MEFV* was a risk factor for systemic onset JIA [15]. This is in line with previous reports on systemic JIA as well.

Finally Gendelman *et al.* [16] addressed the question of whether the chronic inflammation of FMF was associated with ischemic heart disease. The multivariate analysis showed that FMF patients had an increased risk for ischemic heart disease compared with controls [16]. This was attributed to uncontrolled inflammation. As this was a large study, they were not able to assess the compliance with colchicine treatment, comorbidities or the lab values. However, this result cautions us for the need for tight inflammation control in FMF.

ANY NEW DATA IN TREATMENT?

We now have the long-term safety and efficacy data of canakinumab in colchicine-resistant FMF patients, at 113 weeks [17]. This article evaluated 60 patients who received open-label canakinumab (150 or 300 mg) in the last 72 weeks phase of the CLUSTER study. Patients had a good control of disease activity and the median C-reactive protein levels remained in the normal range. However, the serum amyloid A levels remained slightly over the normal level. No new safety signal was reported among the 57 patients who completed the study [17].

Case series for the use of anti-IL6 suggested beneficial effect in FMF. A Japanese group is now conducting an open-label continuation study of tocilizumab in FMF patients resistant or intolerant to colchicine [18]. We await the results of the efficacy and safety of anti-IL6 in FMF.

CONCLUSION

This last year has introduced us some important data, such as the evolutionary selective advantage of MEFV mutations as well as new criteria for classifying the disease. However, FMF still harbors many unanswered questions and continues to challenge us. We still need work to enlighten the many factors affecting the final phenotype in FMF.

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Conflicts of interest

There are no conflicts of interest.

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Safety updates in novel therapeutics for pediatric rheumatic disease

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Purpose of review
Biologics and novel targeted therapeutics have transformed the management of pediatric rheumatic diseases over the past two decades; however, questions about short-term and long-term safety remain. Safety data gathered from recent clinical trials, long-term extensions of prior trials, registries, and other real-world evidence are summarized here for biologics and novel therapeutics commonly prescribed for pediatric rheumatic diseases.

Recent findings
With nearly 20 years of therapeutic experience, tumor necrosis inhibitors (TNFi) are generally well tolerated, although infections, malignancy, and development of new autoimmunity remain a concern. Risk of infections may be higher in IL-1 and IL-6 inhibitors, and lower in abatacept, compared with TNFi. Safety data for B-cell-targeted therapeutics and janus kinase inhibitors are emerging, but remain limited, especially in children.

Summary
Biologic and novel targeted therapeutics offer a promising future for children with pediatric rheumatic disease. However, long-term safety data in children remain limited for several agents. With any therapeutic option, both short-term and long-term safety concerns must be weighed against individual clinical needs when choosing the optimal treatment for each child.

Keywords
biologics, pediatric rheumatic disease, therapeutics

INTRODUCTION

Biologics and novel targeted therapeutics have transformed the management of pediatric rheumatic diseases over the past two decades. Although the oldest biologics now have decades of therapeutic experience and more established safety profiles, most new therapeutics lack extensive and/or long-term safety data, particularly in children. Safety data gathered from recent clinical trials, long-term extensions of prior trials, registries, and other real-world evidence for biologics and novel therapeutics commonly prescribed for pediatric rheumatic diseases are summarized herein.

TUMOR NECROSIS INHIBITORS

Etanercept (ETN) is a fusion protein consisting of the tumor necrosis factor (TNF) receptor and Fc portion of IgG1, which binds and inactivates soluble TNF-α and TNF-β. ETN was the first biologic approved for polyarticular juvenile idiopathic arthritis (pJIA) in patients ages 2 years and older [1].

Recently published trials supporting the short-term safety of ETN in juvenile idiopathic arthritis (JIA) and Kawasaki disease show comparable and generally mild adverse events (AEs) across ETN and nonbiologic therapy groups [2,3]. Long-term safety data include the 6-year follow-up of 109 patients with JIA enrolled in the open-label phase III CLIPPER trial [4], revealing 107 infections per 100 patient-years (100PY), low serious AEs (SAEs) (6/100PY), 1 malignancy, and 10 new autoimmune diseases (7 of which were uveitis) [5]. Eighteen-year follow-up from the BIKER JIA registry reported similar AEs across ETN and biologic-naive groups

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KEY POINTS

- TNFi have the longest track record of use; safety concerns include infections, malignancy, and development of new autoimmune disease.
- Long acting IL-1 inhibitors, such as canakinumab, and IL-6 inhibitors may have a higher risk of infection compared with other biologic agents, but this is based solely on real-world observational data as no head-to-head studies have been performed.
- Abatacept continues to show a reassuring safety profile but infections and new autoimmune events can occur.
- Pediatric-specific safety data for JAK inhibitors, B-cell-targeted therapeutics are limited but current trials and registry collection are underway.

(34/100PY and 36/100PY, respectively), but statistically more SAEs in ETN group (4/100PY compared with 1/100PY for biologic-naive). SAEs included serious infections (including herpes zoster reactivation), new autoimmune disease [inflammatory bowel disease (IBD), uveitis, and psoriasis, although psoriasis risk was not statistcally different from the biologic-naive group], 1 demyelination event, 5 deaths (3 considered not related to ETN), and 8 malignancies (3 with concurrent therapy, 5 with prior ETN exposure, all previously reported) [6▪▪,7]. Additionally, 15 cases of depression and suicidal ideation were reported with ETN, which was higher than the biologic-naive group (0.25 versus 0.05/100PY) [6▪▪], and may warrant further consideration.

Infliximab (IFX) is a chimeric human-mouse monoclonal antibody that binds and neutralizes soluble and transmembrane TNF-α. Unlike the other TNFi, IFX is not currently labeled for use in JIA [8]; however, it is used and studied off-label for many diseases including JIA, uveitis, and Kawasaki disease.

Safety concerns specific to IFX include infusion reactions and greater immunogenicity than fully humanized monoclonal antibodies [8]. A postmarketing surveillance study of 291 children with Kawasaki disease reported adverse drug reactions in 12% (most commonly rash, fever, and infection), 4 infusion reactions, and new autoimmune antibodies in 3 patients [9]. A 2-year registry of 32 patients with JIA-associated uveitis (JIA-U) reported 25/100PY AEs (most frequently infections and headache, with one infusion reaction) but no serious or life-threatening AEs related to IFX [10]. Additionally, IFX was included with other TNFi in a real-world registry study, which revealed a low rate of infections and SAE infections (9 and 1/100PY, respectively) [11▪▪].

Adalimumab (ADA) is a humanized monoclonal antibody that binds TNF-α and blocks interaction with cell surface receptors. ADA is indicated for pJIA and JIA-U in patients 2 years of age and older [12], and is widely used for other JIA subtypes and autoimmune diseases.

Safety findings from seven open-label clinical trials in 577 pediatric patients showed a similar safety profile across ADA treatment indications; and in 274 patients with JIA, 97% reported at least one AE (525/100PY) [13]. The vast majority were minor (mild infections and injection site reactions including injection site pain) [13]. SAEs were less common (14/100PY in JIA), and included new-onset psoriasis (<1/100PY in JIA) and serious infections, such as pneumonia, appendicitis, and herpes zoster [13]. No deaths or malignancies were reported [13]. The randomized, placebo-controlled SYCAMORE trial in JIA-U reported 29/100PY SAEs (compared with 19/100PY in the placebo group); the vast majority were infections [14]. No malignancies, demyelinating diseases, or deaths were reported [14,15▪]. Five-year follow-up of 28 SYCAMORE participants reported a low rate of AEs (37/100PY), most minor viral infections [16].

Recent registry studies show variable safety event rates. Seven-year interim results from the STRIVE Registry reported slightly more AEs and SAEs in arms treated with ADA compared with methotrexate alone (AEs: 43/100PY and 41/100PY, and SAEs: 2/100PY and ≤1/100PY, respectively) [17▪]. Most common AEs were worsening arthritis, infection, and injection site pain [17▪]. Among SAEs, cases of new autoimmune disease including psoriasis were rare but more commonly seen with ADA treatment; no deaths, malignancies, active tuberculosis, or demyelinating events were reported [17▪]. The BIKER registry reported 67/100PY AEs and 5/100PY SAEs in 584 patients with JIA exposed to ADA over 1082PY [18]. No deaths or malignancies were reported during ADA treatment; however, two cases of malignancy reported in patients exposed to ADA in the past were judged unrelated to ADA [18].

Golimumab (GOL) is a humanized monoclonal antibody that binds soluble and transmembrane TNF-α and blocks receptor binding. GOL is the newest TNFi to be approved by the Food and Drug Administration (FDA) for the treatment of pJIA in patients 2 years of age and older [19]. GOL is also used and studied off-label for uveitis.

In an open-label pJIA study, the majority of patients (85%) experienced at least one adverse event (360/100PY), and 7% experienced at least one SAE (8.2/100PY) [20▪]. Sixty-five percent experienced at least one infection, 6% experienced at least one serious infection and one patient

experienced an opportunistic infection. One death from septic shock was reported after the conclusion of the study, likely related to GOL and representing the first reported death with GOL in pediatric rheumatic disease [20▪]. Infusion reactions were rare and there were no reports of active tuberculosis, demyelinating events, or anaphylaxis [20▪].

As a group, TNFi carry a black box warning for infection and malignancy. Specific warnings include tuberculosis, invasive fungal and opportunistic infections, and lymphoma, including an increased risk for hepatosplenic T-cell lymphoma with IFX and ADA used with concurrent immunosuppressive therapies in IBD [21]. However, the association between TNFi and malignancy remains confounded by the increased predisposition for malignancy with various underlying autoimmune diseases and concomitant use of nonbiologic disease-modifying antirheumatic drugs (DMARDs) [22]. Additionally, new-onset autoimmune disease including psoriasis are reported, though overall numbers seem low. Vigilant observation and reporting of these rare but serious outcomes should remain a priority. Decisions to initiate TNFi therapy should consider the clinical scenario, risks, and benefits specific to each patient.

INTERLEUKIN 1 BLOCKADE

Anakinra (ANA) is a recombinant form of the IL-1 receptor antagonist that competitively inhibits receptor binding. ANA is indicated for the treatment of Deficiency of IL-1 Receptor Antagonist and Neonatal-Onset Multisystem Inflammatory Disease [23], but is frequently used and studied off-label for systemic-onset JIA (soJIA), and more recently, Kawasaki disease and novel coronavirus-19 (COVID-19)-associated multisystem inflammatory syndrome in children.

ANA is generally considered well tolerated because of its relatively short half-life, although adult studies reveal serious infections and neutropenia, especially in combination with TNFi [24]. A multicenter retrospective observational study of ANA and canakinumab (CAN) in 475 pediatric and adult patients reported a combined adverse event and SAE rate of 8/100PY (most commonly rash, injection site reactions, hematopoietic disorders, and infections) [25]. Of 13 SAEs reported, there were 3 cases of anaphylaxis with ANA [25], 1 case of mesothelioma not related to treatment, and 5 deaths (4 in adults with disease-related complications and 1 severe bacterial infection) [25]. Real-world data from 105 children treated with ANA and/or CAN in the BIKER registry found a higher incidence rate of infections with IL-1 inhibitors compared with TNFi; however, notable limitations to these data included relatively low numbers and short treatment time-frame [11▪▪].

CAN is a humanized monoclonal antibody that binds interleukin-1β and blocks receptor interaction. CAN is indicated for autoinflammatory Periodic Fever Syndromes and soJIA in patients aged 2 years and older [26].

Infections are the primary safety concern for CAN. Recent open-label studies for soJIA reported high rates of AEs and SAEs (819/100PY and 56/100PY, respectively); however, SAEs were higher in patients with fever at baseline and ongoing glucocorticoid therapy, and notably, adverse event rates decreased over time [27]. One malignancy was reported but was considered unlikely related to CAN [27]. A small open-label study of colchicine-resistant familial mediterranean fever (FMF) reported AEs in 70% of patients (559/100PY); however, the majority (>90%) were mild to moderate and many overlapped with symptoms of FMF flare [28▪]. Six serious infections (sinusitis, cellulitis, gastroenteritis, urinary tract infection, peritonitis, infectious colitis), no opportunistic infections, and no deaths were reported [28▪]. Similarly, an open-label study for cryopyrin-associated peridic syndrome reported at least one adverse event in nearly all patients (most commonly upper respiratory tract infection, nasopharyngitis, and diarrhea) and SAEs in half of the 17 patients who were followed through the 152-week extension phase [29]. Long-term extension (up to 5 years) of the pivotal phase III trials for soJIA reported 797/100PY AEs, most commonly infections [30]. SAEs (41/100PY) were most commonly not only disease flare, MAS, and fever but also included serious infections (10/100PY), including 4 opportunistic infections, 2 of which were suspected related to CAN [30].

INTERLEUKIN 6 BLOCKADE

Tocilizumab (TCZ) is a humanized monoclonal antibody that binds soluble and membrane-bound IL-6 receptors and inhibits pro-inflammatory signaling. TCZ is indicated for the treatment of pJIA and soJIA in patients 2 years of age and older [31], and used and studied off-label in Takayasu arteritis, uveitis, Castleman's disease, autoimmune brain disease, and recently COVID19.

TCZ has a black box warning for serious infections, notable for tuberculosis, invasive fungal infections, and opportunistic infections [31]. The pivotal CHERISH trial in pJIA reported at least one adverse event in 85% of patients (480/100PY), primarily infections including pneumonia, bronchitis, and cellulitis [32]. Twenty-two SAEs were reported in 17 patients (13/100PY) and included benign

intracranial hypertension, uveitis, urinary calculus, pneumonia, and cellulitis, considered related to TCZ, and no deaths or malignancies [32]. Abnormal laboratory parameters (elevated liver enzymes, cytopenias, and elevated cholesterol) were not uncommon [32]. An open-label extension up to 193 weeks in 41 CHERISH participants reported 181/100PY AEs and 7/100PY SAEs (1 case of severe neutropenia; no deaths, malignancies, tuberculosis or demyelinating disorders) [33]. An observational study of 56 pJIA patients up to 24 months reported 201/100PY AEs [34], most frequently upper respiratory infections, otitis media, skin infections, gastroenteritis [34]. SAEs (13/100PY) were most commonly complicated infections; no deaths, malignancies, mycobacterial infection, or new onset autoimmune disease were reported [34]. The German AID registry of 46 patients with soJIA treated up to 48 months reported 22/100PY AEs and 3/100PY SAEs, including 1 case of Hodgkin's lymphoma, 1 case of intestinal perforation, and no deaths [35]. The BIKER registry reported incident infections in TCZ comparable with IL-1 inhibitors but higher than TNFis [11▪▪].

COSTIMULATORY INHIBITORS

Abatacept (ABA) is a fusion protein containing the extracellular domain of the cytotoxic T-lymphocyte-associated antigen-4, which blocks T-lymphocyte activation. ABA is indicated for the treatment of pJIA in patients 2 years of age and older [36].

ABA shows a favorable safety profile in both clinical trials, registry data, and real-world evidence, as reviewed by Brunner *et al.* [37▪]. Clinical trials reported at least one adverse event in 88–100% of patients (173–426/100PY), but SAEs in only 7–20% (4–6/100PY) [37▪]. Most common infections included nasopharyngitis, upper respiratory infections, and influenza [37▪]. Serious infections included appendicitis, limb abscess, impetigo, herpes zoster infection, varicella, and bacterial arthritis [37▪]. One death and two malignancies in two separate ABA trials were deemed unrelated to treatment. Real-world safety evidence in 423 pJIA patients with up to 5 years of follow-up revealed five serious infections (≤1/100PY) and 15 autoimmune events (2/100 PY), including new alopecia areata, uveitis, psoriasis, and IBD [37▪]. One death unrelated to treatment and no malignancies were reported [37▪]. The BIKER registry reported no serious infections in 105 patients with JIA [11▪▪].

JANUS KINASE INHIBITORS

Janus kinase (JAK) inhibitors, including tofacitinib (TFC) and baricitinib, are nonbiologic small molecules that decrease cytokine signaling by preventing activation of signal transducers and activators of transcription proteins. TFC is indicated for active pJIA in patients 2 years of age and older [38], and is increasingly used and studied in a variety of rheumatic diseases.

TFC has a black box warning for serious infections (tuberculosis, bacterial, invasive fungal, and opportunistic infections), malignancy (lymphoma and posttransplant lymphoproliferative disease), thrombosis, and mortality (the latter two for patients 50 years of age and older) [38]. In adults, the safety profile is in line with other biologic DMARDs, but with a potential increased risk of herpes zoster infection [39▪]. The safety profile in children is not well defined. A phase I open label study of 26 patients with pJIA reported a total of four AEs and no serious or severe AEs or deaths [40]. An open-label study of 35 infants and children with Aicardi Goutieres syndrome receiving baricitinib reported two deaths related to complications from the underlying condition [41]. Safety data from a phase III pJIA trial have not been published yet; however, preliminary study data show AEs in 48% of patients in the open-label phase, 65% in the double-blind phase (compared with 67% with placebo), and SAEs in 3% (most commonly infections, diarrhea, and vomiting) as of March 2021 [42].

B-CELL-TARGETED THERAPEUTICS

Belimumab (BEL) is a humanized monoclonal antibody that inhibits binding of B lymphocyte stimulator protein to receptors, thereby disrupting B-cell survival. BEL is indicated for patients with active, autoantibody-positive SLE aged 5 years and older [43].

Primary safety concerns include infections and malignancies, although rates are generally low in adult studies [44–46,47▪]. Additional concerns are infusion reactions, with serious and/or severe infusion reactions in up to 1.2% of adult BEL trial participants [46], and psychiatric events, including serious depression and depression-related events, reported more frequently in adults receiving BEL [46,47▪]. Data in children are scarce; however, neuropsychiatric SAEs, including suicidal ideation and central nervous system vasculitis, were reported in a large multicenter observational study that included 39 patients with pediatric SLE (pSLE) [48]. An ongoing phase II trial in pSLE reported a similar incidence of AEs, including infusion reactions, across treatment and placebo groups, and no deaths, suicidal ideation or behavior events in the treatment group [49▪].

Rituximab (RTX) is a chimeric monoclonal antibody that binds to CD20 and causes B-cell lysis. RTX is indicated for the treatment systemic vasculitis in patients 2 years of age and older, and is used and studied extensively off-label for rheumatic diseases including dermatomyositis, JIA and SLE [50].

RTX has a black box warning for infusion reaction, severe mucocutaneous reactions, hepatitis B reactivation, and progressive multifocal leukoencephalopathy [50]. The Biologics for Children with Rheumatic Diseases observational cohort study reported a serious infection rate of 8/100PY in 41 children with JIA, all occurring 14–115 days following the most recent infusion [51]. Mild infusion reactions occurred in four patients, with no anaphylaxis [51]. Long-term safety in children has not been characterized.

CONCLUSION

Biologics and novel targeted therapeutics have transformed the field of pediatric rheumatology. When selecting from an expanding treatment armamentarium, both short- and long-term safety concerns must be considered. Key concepts to critically assess safety in any new drug include the following. 1, Study design. Randomized placebo-controlled trials, long-term extension studies, registry, and other real-world data provide different rigor, generalizability, and capacity to control for confounding factors. Thus, a thorough safety assessment should be drawn from a broad scope of studies. 2, Extrapolation from adult studies. Although adult data often provide important insights into drug safety, these should never fully substitute for pediatric-specific data. Developmental differences in physiology and expression of drug metabolizing enzymes may affect drug absorption, distribution, metabolism, and excretion and hence, response and toxicity. 3, Current knowledge gaps. There remain significant gaps in understanding the pharmacodynamics, or drug effect on the body, in complex rheumatic diseases. Only time will reveal how biologics and novel targeted therapeutics will modify these diseases long-term. In the meantime, vigilant study and reporting of outcomes on these therapies must continue, in order to provide meaningful data to drive clinical decisions now and in the future.

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Conflicts of interest

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Rheumatology at the center of coronavirus disease 2019: pathogenesis, treatment, and clinical care

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The first case of novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus 2019 (COVID-19), was reported in Wuhan, China in December 2019 [1]. Cases increased exponentially and quickly spread across the globe, reaching pandemic levels and becoming an international health crisis [2]. As of 22 May 2021, there have been 165 772 430 cases of COVID-19 reported to the WHO, including 3 437 454 deaths [3]. The entirety of the healthcare community, including rheumatologists, adapted seemingly overnight to this new medical reality – including reassignment of practitioners to the care of patients with COVID-19 from their normal duties and the heavy reliance on telemedicine to continue routine, maintenance care [4,5].

Rheumatology, perhaps unexpectedly, quickly emerged as a key medical discipline in the fight against COVID-19. In addition to direct redeployment to hospitals for the care of patients with COVID-19, the field took part in a massive undertaking to characterize infection and its impact on our patients. Rapidly, epidemiologic and cohort studies from across the globe emerged, showing that, in general, patients with immune-mediated inflammatory diseases (IMIDs) who developed COVID-19 did not have worse outcomes (i.e. hospitalization and death) compared with non-IMID patients [6–9]. Additionally, while most immunomodulatory therapy had no effect on outcomes, glucocorticoids appeared to increase the risk of hospitalization, while alternatively, tumor necrosis factor inhibitors were found to possibly decrease the risk of poor outcomes [9,10]. These findings allowed practitioners to confidently keep patients with IMID on their medications through the pandemic, likely preventing a heavy burden of disease flares. Importantly, as evidence emerged that many of the poor outcomes from COVID-19 may actually be because of a hyperinflammatory response [11,12] and that immunomodulatory medications may play a role in the treatment of acute infection [13–15], the expertise of rheumatologists became even more essential.

Our understanding of COVID-19 pathogenesis, therapeutics, and prevention has evolved significantly in just 1 year. And yet, even as at least a proportion of the world is finally emerging from the pandemic, important questions are yet to be addressed as they will undoubtedly impact the lives of patients with IMID and the research agenda for years to come.

The notion that viruses can serve as triggers for IMID is not novel. Viral illnesses have been well documented to be the initial drivers for a variety of autoimmune diseases, such as hepatitis C [16] leading to cryoglobulinemia, and HIV promoting psoriasis [17]. Recent studies have shown high rates of autoantibody production in patients hospitalized with COVID-19, including high rates of antinuclear antibody (ANA) positivity and antibodies associated with antiphospholipid syndrome [18,19]. Chang *et al.* found that almost 50% of patients with COVID-19 had at least one autoantibody, some of which may be pathogenic. Furthermore, the development of new antibodies was positively correlated with immune response to SARS-CoV-2 and, when a small cohort of patients with COVID-19 infection was followed longitudinally, one-third of them developed at least one new autoantibody at the second time point [20]. Another small study found that patients can show higher rates of autoantibodies even months after COVID-19 infection [21].

However, it is important to remember that the presence of autoantibodies does not translate directly into clinical autoimmunity. Autoantibodies, especially ANA and rheumatoid factor, are notoriously nonspecific and have been associated with multiple infectious processes (i.e. tuberculosis) without an associated development of IMID [22]. Although there have been case reports of new autoimmune diseases (most notably autoimmune hemolytic anemia and Guillain–Barre syndrome) after infection with SARS-CoV-2 [23], definite causality

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could not be attributed to COVID-19. A recent epidemiologic study from the United Kingdom, for example, found that the incidence of Guillain–Barre syndrome was actually lower in the period between March and May 2020 as compared with this same period in 2016–2019 [24].

Although SARS-CoV-2 has demonstrated a possible cross-reactivity with human tissue [25], there is not sufficient evidence to associate COVID-19 to the triggering of de novo autoimmunity. Long-term studies, many of which are currently underway, are needed to better answer this question.

The rapid development of vaccines for COVID-19 has presented new hope for global recovery from this pandemic. Data regarding the mRNA COVID-19 vaccine safety and efficacy are rapidly emerging for immunocompetent adult populations, where more than 90% of subjects develop adequate humoral response [26]. However, patients with IMID were not included in these original studies despite the fact that these individuals may have an inherently heightened susceptibility to infection. Moreover, the strength of response to viral vaccines (i.e. influenza and hepatitis B) and their long-lasting protective effects in IMID patients taking certain disease-modifying antirheumatic drugs (DMARDs), may not be as robust as it is in the general population following immunization [27–31]. Therefore, it is imperative to better understand the effect of these vaccinations in our patient population.

Although very early studies showed no difference in immunogenicity for patients with IMID [32], further evidence is emerging that specific immunomodulatory treatments, and possibly even IMIDs themselves [33], may reduce immunogenicity. In terms of immunomodulatory therapies, methotrexate [34,35], and rituximab [34,36,37] specifically have been identified as potentially decreasing humoral response to mRNA COVID-19 vaccinations. Mycophenolate mofetil [36,38], identified in the organ transplant literature, may also suppress the humoral response. Additionally, methotrexate was found to reduce the cellular response to the BNT162b2 mRNA vaccine as activated CD8+ T cell and the granzyme B-producing subset of these activated CD8+ T cells were not induced after vaccination in patients on methotrexate, despite being induced in both healthy controls and patients with IMID on other immunomodulatory medications in one cohort [8]. However, despite these findings, it is unclear what antibody level would correspond to vaccine clinical efficacy. Additionally, these patients were followed for generally short periods of time and longer term studies will be needed to assess whether these therapies may delay, rather than prevent antibody response. Critically, confirmation studies will be required to determine whether alternative strategies, such as additional vaccination doses or alteration of immunomodulator treatment dosing, is warranted. This is of particular importance as future immunization boosters against COVID-19 will likely be necessary.

As we move past the 1-year mark of the pandemic, studies found that even months after recovering from COVID-19, many patients continue to experience symptoms, such as fatigue, dyspnea, joint pain, muscle weakness, chest pain, and cough [39,40]. This new syndrome has now been dubbed *long haul COVID-19*. Although many of these patients are being evaluated by rheumatologists, the underlying pathophysiology of this syndrome remains unclear. Hypothesized mechanisms include: virus-specific changes, organ damage or inflammation because of acute infection, new autoimmunity because of immunologic aberration or tolerance breakdown because of acute infection, post critical illness sequalae, or, possibly, a completely unknown mechanism [41].

Currently, these patients require multidisciplinary care and urgent translational and epidemiologic studies are needed to explore the extent and underlying cause of this syndrome. If an immune-mediated inflammatory cause is identified, rheumatologists will again play a central role in the management of these patients. Furthermore, clinical trials using immunomodulators are also likely given their current role in acute infection, and with our knowledge and experience with the chronic use of these medications, rheumatologists will be needed to lead these endeavors.

As we look toward the future, we want to acknowledge patients across the globe who have participated in our studies during this particularly difficult year and the researchers who redirected their time and efforts to understanding and treating COVID-19. Our rapid accumulation of knowledge has allowed us to treat our patients more effectively. Indeed, over the course of the pandemic, rheumatologic patients have seen lower rates of hospitalization, higher level of care, mechanical ventilation, and even death [42]. As we our turn attention to the long-term effects of COVID-19 and vaccination strategies, this should also help us expand our knowledge of the interaction between infectious disease, immunology, and autoimmunity, and provide renewed insights into pathogenesis and therapeutic targets.

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Conflicts of interest

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Coronavirus disease 2019: update on coronavirus disease 2019 outcomes and vaccine efficacy in patients with immune-mediated inflammatory disease

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Purpose of review
Although the literature to date on COVID-19 outcomes in those with immune-mediated inflammatory disease has been largely reassuring there remain many unanswered questions. These include the impact of specific medications on outcomes and the antibody response after COVID-19 vaccination.

Recent findings
We summarized the current literature related to COVID-19 outcomes in immune-mediated inflammatory diseases in rheumatology, gastroenterology, dermatology, and neurology. Overall, we found either no difference or modest differences in risk for severe COVID-19 for people with immune-mediated diseases compared with the general population. When considering disease-specific factors, glucocorticoid use and underlying immune-mediated disease activity were generally associated with worse outcomes. Specific medications varied in associations: tumor necrosis factor inhibitors generally had lower odds for severe COVID-19 outcomes, whereas rituximab use generally had higher odds for severe outcomes. We also detailed the recent reports of antibody response to COVID-19 vaccination in people with immune-mediated inflammatory diseases.

Summary
Investigations of immune-mediated inflammatory diseases across several organ systems have offered important insight into the COVID-19 disease course. Overall, these studies have provided reassurance to patients and clinicians while also identifying groups who may be at higher risk for poor outcomes.

Keywords
coronavirus disease 2019, dermatology, gastroenterology, neurology, outcomes, rheumatology

INTRODUCTION

The novel coronavirus pandemic continues to have a tremendous impact on our daily life, particularly in those with immune-mediated disease. This is because of altered immunity from underlying disease and immunomodulating medications. The impact of the pandemic on outcomes has been described previously but constantly evolving information makes regular updates mandatory [1–3]. International collaborative studies, such as the COVID-19 Global Rheumatology Alliance and SECURE-IBD have efficiently generated timely data that has informed the rheumatology community [4–7,8▪▪,9▪▪].

There is clear relevance to reviewing immune-mediated diseases across specialities as many therapies are used widely, for example, targeted cytokine inhibitors and B-cell depletion therapies are used across rheumatology, dermatology, gastroenterology and neurology. With increasingly large datasets being collected and randomized controlled trials of many immunosuppressing therapies in coronavirus

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KEY POINTS

- Broadly relevant risk factors, such as age, sex and comorbidity are important for determining outcomes in patients with immune-mediated diseases.
- Disease-specific risk factors influencing outcomes include elevated disease activity and medications, such as rituximab.
- Many immunomodulating medications reduce the response to COVID-19 mRNA vaccines and some, such as rituximab seem to dramatically reduce the response.

disease 2019 (COVID-19) being completed, we are building a better picture of both the risks and benefits of immune-mediated therapies [10]. With more time and information, it is becoming clear that the risk factors that apply to the general population like age, sex, and comorbidity are critically important to outcomes in patients with immune-mediated disease. Although there are clearly some therapies that seem to stand out for their increased risk, for example, rituximab, the burden of increased risk can be attributed to risk factors that are widely relevant across all those in the community [11,12▪▪].

RHEUMATIC DISEASES

Rheumatic diseases are broadly characterized by autoimmunity, systemic inflammation and fibrosis – also identified to be prominent features of COVID-19 even early in the pandemic [13,14]. Throughout the pandemic, there has been intense interest in repurposing immunomodulatory medications, such as hydroxychloroquine, tocilizumab and baricitinib as therapies for COVID-19 [10,15,16]. Some rheumatic disease manifestations, such as interstitial lung disease and acquired comorbid conditions, such as cardiovascular disease may place people with rheumatic diseases susceptible to infection and poor outcomes from COVID-19 [11,17]. Thus, studying the intersection of rheumatic diseases and COVID-19 has been of intense interest. However, this also offered challenges as rheumatic diseases are both uncommon and heterogeneous.

One of the first reports of rheumatic disease and COVID-19 was a case series mostly consisting of inflammatory arthritis who seemed to mostly have a mild disease course [18]. Another case series showed that most people with systemic lupus erythematosus (SLE) did not develop COVID-19 and only a very few had poor outcomes [19]. However, two comparative studies suggested that rheumatic disease patients may be at increased risk for mechanical ventilation compared with general population controls [20,21]. Risks for hospitalization and mortality were similar in both of those small studies. In a large nationwide English study OpenSAFELY, people with rheumatoid arthritis (RA), lupus, or psoriasis were identified to have a modest but statistically significantly increased risk for mortality (hazard ratio 1.19) [11]. However, the identification of these diseases using administrative codes alone may be prone to misclassification and the three conditions are quite heterogeneous. Thus, the associations of specific rheumatic diseases with COVID-19-related mortality is not clear. A large study analyzed multiple electronic health records compared people with rheumatic disease to age-matched and sex-matched comparators [12▪▪]. This study found that people with rheumatic diseases were at increased risk for many poor outcomes including hospitalization, intensive care unit admission, acute kidney injury and venous thromboembolism [12▪▪]. Most associations were attenuated or eliminated after adjustment for comorbidities, suggesting that these mediated the relationship between rheumatic diseases and poor COVID-19 outcomes.

These studies were mostly performed early in the pandemic when hospital systems were commonly overwhelmed and the clinical benefits of drugs, such as remdesivir and dexamethasone were not yet established [22,23]. Two studies showed that the excess risk of mechanical ventilation and other poor COVID-19 outcomes improved over calendar time [24,25]. This suggests that people with rheumatic disease may have similar outcomes to the general population later in the pandemic now with effective treatments and health system capacity. A nationwide study in Sweden showed that the excess relative risk of mortality for RA and other inflammatory joint diseases was relatively stable in 2020 compared with earlier years [26]. People with RA or other inflammatory joint diseases had slightly higher rates of severe COVID-19 outcomes, such as hospitalization, ICU admission, and mortality but these were infrequent and generally not statistically different than general population comparators [26]. Another matched comparative study of hospitalized patients suggested that severe COVID-19 outcomes were more common in connective tissue diseases, such as SLE than general population controls; inflammatory arthritis had similar outcomes to their controls [27]. A meta-analysis reported that autoimmune disease patients had two-fold odds of COVID-19 than controls [28]. Overall, the current literature suggests that rheumatic diseases may modestly increase risk of severe COVID-19 compared with the general population.

The COVID-19 Global Rheumatology Alliance (GRA) formed early in the pandemic and allowed

physicians to voluntarily enter cases of COVID-19 in rheumatic patients [4–6]. After an initial, early descriptive report of 110 patients, the first large GRA paper with 600 patients investigated risk factors for hospitalization among rheumatic patients [29▪,30]. This verified general population risk factors for severe COVID-19, such as older age and comorbidities [29▪]. This also showed that baseline use of glucocorticoids were associated with increased odds of hospitalization [29▪]. Importantly, biologic and targeted synthetic disease-modifying antirheumatic drugs (DMARDs), particularly tumor necrosis factor inhibitors (TNFi) were associated with lower odds of hospitalized COVID-19 compared with no DMARDs [29▪]. Other reports also support this finding seen with TNFi [31]. Similar findings implicating glucocorticoids with worse COVID-19 outcomes were reported in a large single-center study in New York City [32]. This offered early reassurance to patients and clinicians that use of these medications were not clearly associated with poor outcomes.

A more recent, larger GRA study that included 3729 patients showed that higher baseline rheumatic disease activity was associated with higher odds of COVID-19-related mortality [33▪▪,34]. This study also showed that rituximab and sulfasalazine were each associated with higher odds of COVID-19-related mortality than methotrexate monotherapy. In another French cohort study, rituximab use in rheumatic diseases was also associated with higher risk of severe COVID-19 outcomes than rheumatic diseases not treated with rituximab [35]. These poor outcomes may be because of prolonged SARS-CoV-2 infection related to B-cell depletion and impaired antibody response. Some reports have suggested that immunocompromised patients, particularly those on rituximab, may be a reservoir for prolonged SARS-CoV-2 infection that may result in accelerated viral evolution that has resulted in variants that could increase virulence and evade vaccination efforts [36]. Thus, rheumatic patients and other immunocompromising states are likely to remain a central player as the pandemic continues to unfold. Finally, the differences in outcome based on race and ethnicity seen in the wider population has also been reflected in the rheumatic disease population, likely mediated by multiple medical and nonmedical factors [37].

GASTROENTEROLOGY

In contrast to rheumatic diseases, inflammatory bowel diseases (IBD), such as Crohn's disease and ulcerative colitis have relatively less heterogeneity. A recent large nationwide population-based matched retrospective study in Sweden showed that IBD patients were significantly more likely to be hospitalized for COVID-19 than matched comparators [38]. Another nationwide Danish study identified IBD patients with COVID-19 and compared with a population-based cohort [39]. This study found that IBD patients had lower prevalence of COVID-19 than the general population, offering reassurance but was limited by small numbers of IBD patients [39]. In a meta-analysis of 24 studies, SARS-CoV-2 infection risk in patients with IBD was similar to the general population [40]. COVID-19 outcomes for IBD patients were worse in ulcerative colitis compared with Crohn's disease.

Gastroenterologists formed a physician registry called Surveillance Epidemiology of Coronavirus Under Research Exclusion for IBD (SECURE-IBD) early in the pandemic, which was a model that the GRA adapted. The initial report in SECURE-IBD reported higher odds of hospitalization for COVID-19 in patients on baseline glucocorticoids and lower odds for IBD patients on TNFi [9▪▪]. A larger follow-up study reported that thiopurine monotherapy or in combination was strongly associated with severe COVID-19 outcomes compared with TNFi monotherapy [8▪▪]. This offered further reassurance to the safety of biologic DMARDs, such as TNFi as this finding has been observed across several diseases and organ systems [31]. It is not currently clear whether these findings are because of a possible protective effect of TNFi or whether the findings may be confounded. Trials are underway to investigate possible efficacy of TNFi for treating COVID-19 [41,42]. Another large study identified all people with IBD in the Veterans Affairs Healthcare System and found that vedolizumab and glucocorticoids were associated with severe COVID-19 outcomes [43].

Overall, the experience of IBD during the COVID-19 has mostly offered reassurance that patients have at best modestly increased risk for severe outcomes compared with the general population. The outcomes of those on TNFi also provides reassurance that this class of medication may be safely continued. Conversely, other medications used in IBD, such as glucocorticoids, thiopurines, and vedolizumab may be associated with more severe COVID-19 outcomes.

DERMATOLOGY

As in rheumatology and gastroenterology, there has been great interest and concern in the dermatology community concerning the risk of COVID-19 in patients with psoriasis, atopic dermatitis, and other immune-mediated conditions. As in rheumatology, early concern was informed by findings from the

OpenSAFELY population-based study in England, which reported a 20% higher risk of COVID-19 death among patients with RA, lupus, or psoriasis (hazard ratio 1.19), a large, heterogeneous group [11]. Two large cohort studies sought to evaluate the risk of COVID-19 infection in patients with psoriasis compared with the general population. In one study, investigators estimated the incidence of COVID-19 in patients with psoriasis on systemic therapies in a previously established large, multicenter prospective cohort study [44]. Compared with the general population estimate, the investigators reported a nonstatistical significant trend toward a higher standard incidence rate for COVID-19 infection [SIR 1.58, 95% confidence interval (CI) 0.98–2.41]. Among other limitations, the number of confirmed infections ($n = 21$) and severe outcomes ($n = 13$ hospitalized, $n = 1$ death) was relatively small, which limited the study's power to estimate SIRs for infection and outcomes, such as hospitalization and death. Reassuringly, in a similar study conducted in a prospective psoriasis cohort in Italy, investigators found that psoriasis patients did not have a higher SIR for COVID-19 hospitalization or death [45]. In that study, the investigators also found no association between biologic DMARD use and a higher SIR compared with the general population. However, the number of infections was similarly small in this Italian cohort study as in the Spanish cohort study. Both studies were limited by their reliance on standardized incidence rates, which may not account for other potential confounders of the association of psoriasis with COVID-19 risk and outcomes.

In addition to prospective cohort studies, two physician-reported registries were established early on by the dermatology community. The design of SECURE-AD (atopic dermatitis) and PsoProtect (psoriasis) are similar to the SECURE-IBD and GRA registries previously discussed. The findings from the SECURE-AD registry will be particularly interesting because of the unique treatments used in atopic dermatitis compared with those used in psoriasis, IBD and rheumatic diseases. At the time of this publication, results from SECURE-AD have not yet been published. In contrast, results from the first 374 patients in the physician-reported PsoProtect registry confirmed several observations reported by the GRA and SECURE-IBD registries [46▪]. First, similar risk factors for worse disease were observed in the psoriasis population as in the general population, including older age, male sex, nonwhite ethnicity and comorbid lung disease. Second, patients who used biologic therapies had a 65% lower risk of hospitalization compared with those using nonbiologic therapies.

Observed differences in outcomes according to DMARD use in SECURE-IBD prompted the investigators to explore factors that may contribute to differences in outcomes according to treatment. In an analysis of 1626 patients who reported their experiences during the pandemic to a patient-facing psoriasis registry, patients on biologic treatments were 39% more likely than those on nonbiologic DMARDs to practice shielding (OR 1.39, 95% CI 1.23–1.56) [47]. These findings highlight the caution with which one should interpret estimates of the risk of COVID-19 in patients on various DMARDs as shielding practices may have differed between users of different treatments.

NEUROLOGY

Multiple sclerosis, myasthenia gravis and other neurological diseases, such as autoimmune encephalitis are all managed with immunosuppression, so, neurology faces similar challenges to rheumatology, dermatology and gastroenterology. To add a complicating factor, it has become evident that COVID-19 infection has numerous neurological manifestations [48].

French data in 347 multiple sclerosis patients demonstrated male gender, comorbidities and higher disability as measured by the Expanded Disability Severity Scale score (EDSS) were associated with worse COVID-19 outcome measured with a 7-point ordinal scale [49]. Of broader interest in the context of the hyper-inflammation of COVID-19, a higher proportion of multiple sclerosis patients not on disease-modifying therapy (DMT, 46%) developed severe COVID-19 compared with those taking DMT (16%) [10]. In univariate analysis, DMT therapies were protective of poorer outcomes but this finding was not evident in the multivariate model, noting the limitation of small numbers in this analysis.

B-cell-depleting agents are potentially a risk for poorer outcomes based on patients with rheumatic disease. There were 51 suspected or confirmed cases of COVID-19 found in the B-cell-depleting agent ocrelizumab multiple sclerosis clinical trials up until the end of July 2020 [50]. Disease severity was asymptomatic, mild or moderate in 68.6% and severe in 19.6%, with 6% dying and 6% outcome data missing. Of the total group, 31.4% were hospitalized. In the manufacturer postmarketing surveillance safety database, there were 307 postmarketing cases of COVID-19 with 86% ($n = 263$) confirmed and 14% suspected [50]. Of those 33% were hospitalized and 47% had asymptomatic, mild or moderate disease, with 6% dying.

As of mid-July 2020 in the OPTUM COVID-19 database there were 357 multiple sclerosis patients with confirmed COVID-19 [50]. There were 48 of these patients treated with ocrelizumab and 309 not treated with ocrelizumab. The outcomes were similar between the two groups with 76% and 75% hospitalized in the non-ocrelizumab and ocrelizumab groups, respectively. There were 1.6 and 2.1% who received invasive ventilation in the non-ocrelizumab and ocrelizumab groups, respectively. Finally 3.9 and 2.1% died in the non-ocrelizumab and ocrelizumab groups, respectively.

There have been other small case series published on other neurological diseases, such as myasthenia gravis where older patients made up 75% of the deaths again supporting the premise that widely relevant risk factors remain critical in disease subgroups we worry about [51]. In summary, the small size of the reported cohorts limits the conclusions that can be drawn but specific therapies, such as B-cell-depleting therapies remain a concern, but not to the exclusion of the broadly relevant demographic and comorbidity risk factors.

VACCINE EFFICACY

The quick development of well tolerated and effective COVID-19 vaccines has not only been a tremendous scientific advance during the pandemic but also raises important questions about the efficacy of vaccination in patients with immune-mediated diseases, especially those on immunomodulation. Previous studies have established that several DMARD classes may be associated with a less robust immune response to vaccines for influenza, pneumococcus and other infections [52]. Unfortunately, patients with immune-mediated inflammatory conditions and those on immunomodulation were generally excluded from the initial COVID-19 vaccination trials leaving providers and patients with little guidance on how or when to vaccinate patients on DMARDs. Several reports have not only described a potentially dampened antibody response to SARS-CoV-2 mRNA vaccines among DMARD users but also highlight that the response likely varies across DMARD classes [53,54▪▪,55].

In the largest study to date, 133 adults with autoimmune diseases, including IBD (31.6%), RA (28.6%), spondyloarthritis (15%) and lupus (11%) were included [54▪▪]. Though the antibody response to two doses of SARS-CoV-2 mRNA vaccines was robust among many with autoimmune diseases, it was three-fold lower than the response observed in healthy controls. Similar reductions were observed in the neutralization activity of SARS-CoV-2 antibodies. In particular, glucocorticoid users, Janus Kinase inhibitor users, antimetabolite users and especially those with recent B-cell-depleting therapy exposure had significant reductions in antibody responses. Reductions in the antibody response among patients using TNF inhibitors were more modest.

Similar observations were made in a study of 123 patients with rheumatic diseases, including inflammatory arthritis (28%), lupus (20%) and Sjogren's syndrome (13%) [53]. Though 74% of patients had a detectable antibody response, a median of 22 days after the first dose of an mRNA vaccine, antibody responses were variable across DMARD classes. For instance, while nearly all TNFi users ($n = 16$ of 17) and methotrexate users ($n = 10$ of 13) had an antibody response, rituximab ($n = 2$ of 6) and mycophenolate mofetil ($n = 3$ of 11) users less often had an antibody response. The sample size of this study was small, limiting conclusions that can be drawn, especially as the response was assessed only after the first dose.

A report from a cohort of patients with a history of solid organ transplantation on medications commonly used (e.g. glucocorticoids, azathioprine, mycophenolate) described poor vaccine efficacy after the first dose of an mRNA vaccine [55]. Notably, those on mycophenolate mofetil, mycophenolic acid or azathioprine had a particularly poor response to the vaccine with only 9% mounting an antibody response following the first dose. Caution is needed whenever interpreting these data; however, as the generalizability of these findings to those with immune-mediated conditions is unclear and the immune response was only assessed following the first dose of the mRNA vaccine series, which typically includes two doses.

Additional studies are urgently needed to better define the efficacy of mRNA and other vaccines in each DMARD class, across different vaccine classes, the durability of the antibody response, the T-cell response to vaccination in this population, and the appropriate timing of vaccination in relation to DMARD use.

CONCLUSION

Patients with immune-mediated inflammatory disease have offered important insight into the COVID-19 disease course. Findings have generally suggested either no or modest differences in severity of COVID-19, which provides reassurance to patients and clinicians. However, subgroups of patients may be susceptible to poor outcomes, in particular, patients on rituximab as well as those requiring glucocorticoids because of elevated underlying disease activity. Some evidence suggests that immunocompromised patients may have prolonged viral

infection that may result in viral evolution resulting in SARS-CoV-2 variants. COVID-19 vaccinations offer the possibility to protect immune-mediated inflammatory disease patients. However, the underlying altered immunity and immunomodulator use may blunt vaccine response.

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Is severe COVID-19 a cytokine storm syndrome: a hyperinflammatory debate

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Purpose of review
The COVID-19 pandemic is a global public health crisis with considerable mortality and morbidity. A role for cytokine storm and therapeutic immunomodulation in a subgroup of patients with severe COVID-19 was proposed early in the pandemic. The concept of cytokine storm in COVID-19 has been criticised, given the lack of clear definition and relatively modest cytokinaemia (which may be necessary for viral clearance) compared with acute respiratory distress syndrome and bacterial sepsis. Here we consider the arguments for and against the concept of cytokine storm in COVID-19.

Recent findings
Several criteria have been proposed to identify the subgroup of COVID-19 patients exhibiting a cytokine storm. The beneficial effects of corticosteroids and interleukin-6 inhibition suggest that inflammation is a modifiable pathogenic component of severe COVID-19. The presence of genetic polymorphisms and pathogenic auto-autoantibodies in severe COVID-19 also suggests a significant contribution of immune dysregulation to poor outcomes.

Summary
Hyperinflammation is a key component of severe COVID-19, residing underneath the cytokine storm umbrella term, associated with poor outcomes. Better understanding of the aetiopathogenesis, with identification of biomarkers to predict treatment responses and prognosis, will hopefully enable a stratified and ultimately precision medicine approach.

Keywords
COVID-19, cytokine storm syndromes, hyperinflammation

INTRODUCTION

The COVID-19 pandemic is a major global public health crisis with considerable mortality and morbidity that has exposed complex clinical, scientific and philosophical challenges. The clinical spectrum of COVID-19 ranges from mild, self-limiting symptoms in the majority of cases, to its most severe form manifesting as acute respiratory distress syndrome (ARDS) with multiorgan system failure, the requirement for mechanical ventilation and high risk of death. Initial reports from Wuhan, China demonstrated that some patients with COVID-19 exhibited clinical deterioration at approximately day 10 following symptom-onset, in association with a declining viral load [1], leading to the hypothesis that pathology is driven by an overexuberant inflammatory response, rather than direct viral injury [2▪▪]. A biphasic model of COVID-19 was proposed [3], with an initial viraemic phase, followed by a host hyperinflammatory phase in a subgroup of patients with a self-amplifying, dysregulated immune response associated with high mortality. Despite paucity of data, at an early stage in the pandemic, we recommended evaluating for virally driven hyperinflammation, 'cytokine storm syndrome', in patients with severe COVID-19 and proposed that immunomodulation in this subgroup of patients might reduce the high mortality [2▪▪]. This was prompted by observations that predictors of fatality in COVID-19 included ferritin and interleukin (IL)-6 [4] and early reports of IL-6 inhibition with tocilizumab (off-

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KEY POINTS

- Although the majority of COVID-19 patients experience either too weak of an immune response or an appropriate immune response, a small fraction of patients who go on to develop severe COVID-19 experience hyperinflammation.
- Hyperinflammation in severe COVID-19 resides under the umbrella term of cytokine storm and can be identified using recently described clinical and laboratory criteria.
- Corticosteroids and interleukin (IL)-6 inhibition can reduce mortality in severe COVID-19, suggesting that inflammation is a modifiable pathogenic component of severe COVID-19.
- Other host factors also have significant contribution to poor outcomes in severe COVID-19, including genetic polymorphisms and auto-autoantibodies directed against interferons and other proteins.
- More research is needed to identify specific cytokines and determine appropriate thresholds for cytokine storm and predictive biomarkers of effective therapeutics in the setting of COVID-19 and beyond.

label) demonstrating an efficacy signal. Despite global recommendations against the routine use of corticosteroids early in the COVID-19 pandemic due to worsening outcomes with previous pandemics (severe acute respiratory distress syndrome [SARS] and middle east respiratory syndrome) we found corticosteroids were being used at very high numbers with anecdotal benefits [5▪]. The urgent need for effective treatments to address the rising mortality and anecdotal benefits with immunosuppressive therapies provided impetus to accelerate clinical trials of immunomodulatory agents to target hyperinflammation at a remarkable pace. Following a series of randomized controlled trials demonstrating efficacy, dexamethasone (not formally approved for COVID-19) and tocilizumab (IL-6 blockade; not formally approved for COVID-19) are now standard of care in the treatment of severe COVID-19 and JAK1/2 inhibition with baricitinib (not formally approved for COVID-19) has emergency use authorization from the US FDA. Despite these results and correlative studies revealing immune activation, the concept of cytokine storm in COVID-19 continues to spur significant debate. Critics have questioned the definition of cytokine storm including the threshold levels of cytokines and raised concerns that the term may have distracted focus (e.g. from antiviral strategies or immune stimulants). Concerns were raised regarding the risks of immunosuppression with potential viral resurgence from a reservoir (albeit at low level) as well as super-infections in a heterogeneous patient population and that hypercytokinaemia may be a necessary physiological response required for antiviral immunity and viral clearance [6▪▪].

Here, we consider the features for and against the concept of COVID-19-cytokine storm and potential future directions that may help personalise disease management.

OVERVIEW OF CYTOKINE STORM

Terminology of hyperinflammatory disorders has been the subject of much debate [7–9] even prior to the advent of COVID-19. Cytokine storm is an umbrella term encompassing several hyperinflammatory disorders of immune dysregulation characterized by constitutional symptoms, systemic inflammation, and multiorgan dysfunction that can lead to multiorgan failure and death if inadequately treated. These hyperinflammatory disorders include pathogen-induced, neoplasia-induced, monogenic, and iatrogenic causes. Two representative cytokine storm disease groups are haemophagocytic lymphohistiocytosis (HLH) and multicentric Castleman disease (MCD). HLH, usually manifesting with cytopenia and organ dysfunction, can occur due to genetic defects (primary HLH) or be triggered by infection, rheumatic disorders, and malignant disease (secondary HLH). The cytokine and chemokine storm often including IL-6 in MCD can occur due to uncontrolled infection with human herpesvirus-8 (HHV-8-associated MCD), a monoclonal plasma cell population (POEMS-associated MCD), or for an idiopathic cause (iMCD) [10]. Though these and other cytokine storm disorders share common clinical, immunological, and pathological abnormalities, treatments differ substantially. For example, extremely high IL-6 levels are found in CRS post-CAR-T cell therapy and IL-6 receptor blockade (tocilizumab) is highly effective in treating CART-CRS and iMCD, whereas anti-IL-1 is often preferred in HLH/MAS secondary to underlying rheumatic disease [8].

The aetiopathogenesis of cytokine storms is not fully understood but is thought to occur as a result of inappropriate recognition (e.g., autoinflammatory disorders) or ineffective recognition with immune evasion (e.g., EBV-associated HLH), an inappropriate response with an exaggerated effector response and cytokine production (e.g., chimeric antigen receptor [CAR] T cell therapy) or an ineffective response due to immune evasion (e.g., sepsis), or failure to return to homeostasis (e.g., primary HLH). With each of these triggers, there is a failure of negative feedback mechanisms (e.g., regulatory cell types, decoy receptors, anti-inflammatory

cytokines) that are supposed to prevent hyperinflammation and the overproduction of inflammatory cytokines and soluble mediators, leading to multiorgan failure. Specific pathological cell types differ between cytokine storm disorders, but often include T cells, neutrophils, macrophages, and NK cells. Although a number of cytokines are elevated and signalling pathways are activated in these hyperinflammatory states, the effectiveness of Interferon-γ, IL-1, IL-6, TNF, IL-18, JAK, mTOR, and MAPK inhibitors suggest that they are central to pathogenesis [11,12,13▪▪].

Given the lack of a single formal definition of cytokine storm [6▪▪], and disagreement about how these disorders with an excessive, harmful immune response differ from an evolutionarily acceptable, appropriate inflammatory response in response to a pathogen, e.g. the severe acute respiratory coronavirus 2 (SARS-CoV-2), we recently proposed the following three criteria [13▪▪] for identifying a cytokine storm:

(1) Elevated circulating cytokine levels
(2) Acute systemic inflammatory symptoms
(3) Either secondary organ dysfunction (often renal, hepatic, or pulmonary) due to inflammation beyond that which could be attributed to a normal response to a pathogen (if a pathogen is present), or any cytokine-driven organ dysfunction (if no pathogen is present).

Given the dearth of available evidence, this definition deliberately does not propose a specific threshold for elevations in cytokine levels above the normal range, and we do not recommend specific cytokine panels or mandate individual cytokines that are essential for diagnosis [13▪▪].

COVID-19 CLINICAL COURSE

Infection with SARS-CoV-2 can result in a range of clinical courses from asymptomatic infection to a more classic respiratory infection to multiorgan system dysfunction that would meet our definition of cytokine storm. In Fig. 1, we propose a framework for this heterogeneous host immune response vs virus interaction that is supported by data from randomised controlled trials.

CYTOKINE LEVELS IN COVID-19

One of the strongest sources of dissent regarding the concept of COVID-19 cytokine storm, relates to the only modest elevation in circulation of one specific cytokine out of hundreds: IL-6. A systematic review and meta-analysis of studies in patients with severe or critical disease, where IL-6 levels were recorded included 25 COVID-19 studies ($n = 1245$ patients) with comparator groups including four trials each in sepsis ($n = 5320$), CRS ($n = 72$) and ARDS unrelated to COVID-19 ($n = 2767$) [14]. In patients with severe or critical COVID-19, the pooled mean serum IL-6 concentration was 36.7 pg/mL (95% CI 21.6–62.3 pg/mL; $I^2 = 57.7\%$). Mean IL-6 concentrations were nearly 100 times higher in patients with cytokine release syndrome (3110.5pg/mL, 632.3–15,302.9 pg/mL; $P < 0.0001$), 27 times higher in patients with sepsis (983.6 pg/mL, 550.1–1758.4 pg/mL; $P < 0.0001$), and 12 times higher in patients with ARDS unrelated to COVID-19 (460 pg/mL, 216.3–978.7 pg/mL; $P < 0.0001$). Furthermore, a recent study demonstrated that only a small proportion of COVID-19 patients exhibited a cytokine profile considered by the authors to be consistent with cytokine storm and though several cytokines (including IL-6) were associated with mortality, the levels of these cytokines were in a similar range as patients with seasonal influenza [15]. However, data from iMCD demonstrate that the level of circulating IL-6 is not a reliable predictor of response to IL-6 inhibition with some patients with low IL-6 levels benefitting from siltuximab and others with very elevated IL-6 levels not responding [16,17].

Several studies have shown that patients with severe COVID-19 do indeed have elevated cytokine levels, meeting the proposed definition of cytokine storm syndromes. Longitudinal immunological correlates of disease outcomes demonstrated distinct signatures of 'immunological misfiring' in COVID-19 [18]. The immune profiles of patients with moderate disease (admitted to hospital who survived and did not require intensive care admission) were enriched with tissue reparative growth factors, such as epidermal growth factor, platelet-derived growth factor and vascular endothelial growth factor, with low expression of inflammatory cytokines, whereas patients with severe disease (those who died or required ICU admission) had highly elevated pro-inflammatory cytokines including IL-1α, IL-1β, IL-6, IL-18 and TNF [18]. Analysis from 471 hospitalised patients and 39 outpatients with mild disease demonstrated IL-6, granulocyte colony stimulating factor (GM-CSF) and CXCL10 was associated with severity and accompanied by elevated markers of endothelial injury and thrombosis [19]. Principal component network analysis demonstrated central roles for IL-6 and GM-CSF in COVID-19 pathogenesis. Interestingly comparison with historical influenza samples, showed that IL-6 was equally elevated in both conditions, whereas GM-CSF was prominent only in COVID-19 [19]. Surprisingly, investigational cytokine removal with CytoSorb led to worsening outcomes in critically ill patients on

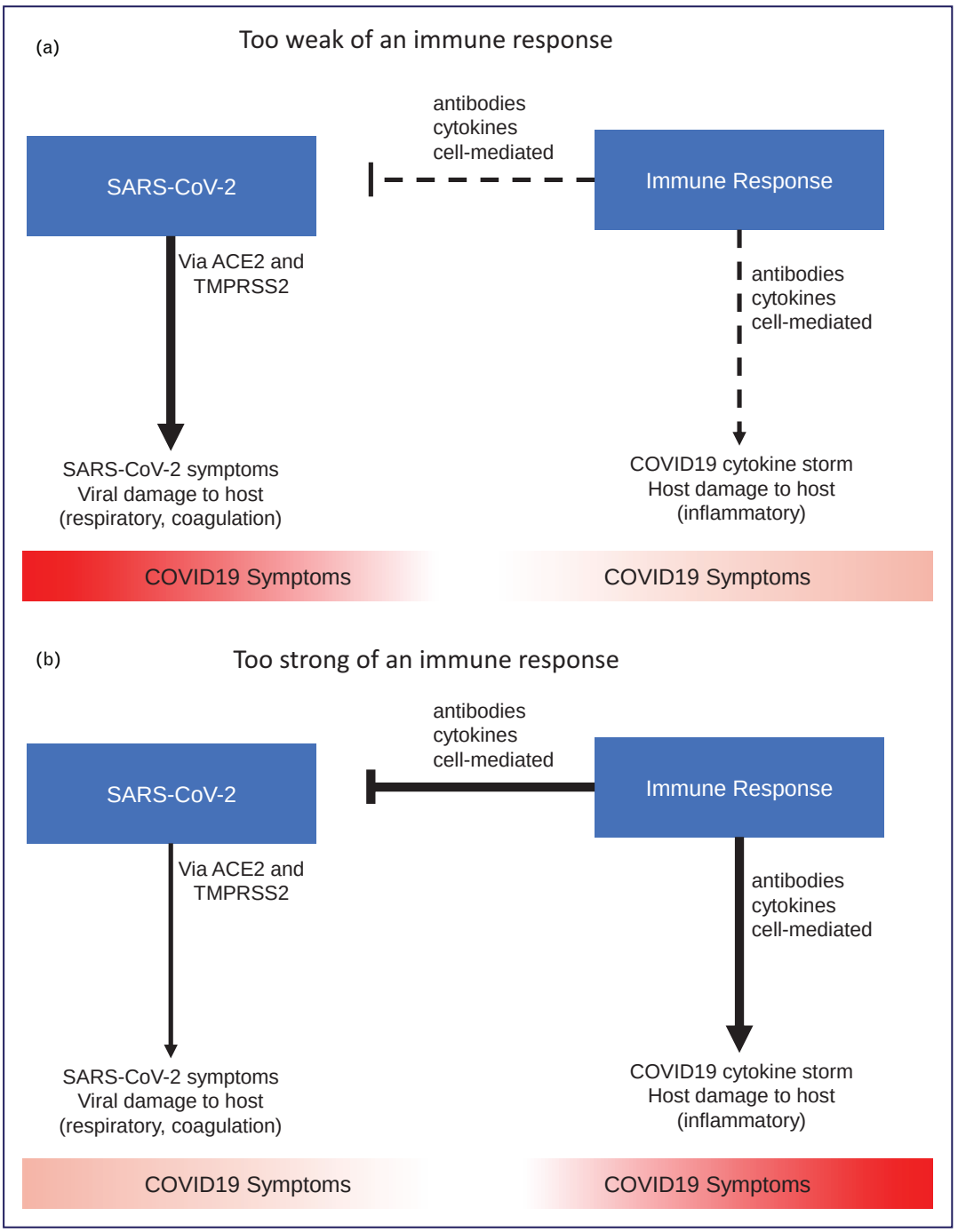

FIGURE 1. A framework for the heterogeneous host immune response in COVID-19. (A) In patients with too weak of an immune response, poorly controlled viral infection leads to direct SARS-CoV-2 related symptoms. (B) In patients with too strong of an immune response, viral damage is mitigated but antibodies, cytokines, and cell-mediated factors contribute to inflammatory symptoms. (C, D) The optimal response can require antivirals, neutralizing antibodies, and immune stimulants early in the disease course when patients may be mounting too weak of an immune response due to genetic factors or auto-antibodies against interferons. Alternatively, the optimal response may require antithrombotics and immunosuppressants late in the disease course when patients are mounting too strong of an immune response involving hyperinflammation and hypercoagulation. SARS-CoV-2, severe acute respiratory coronavirus 2.

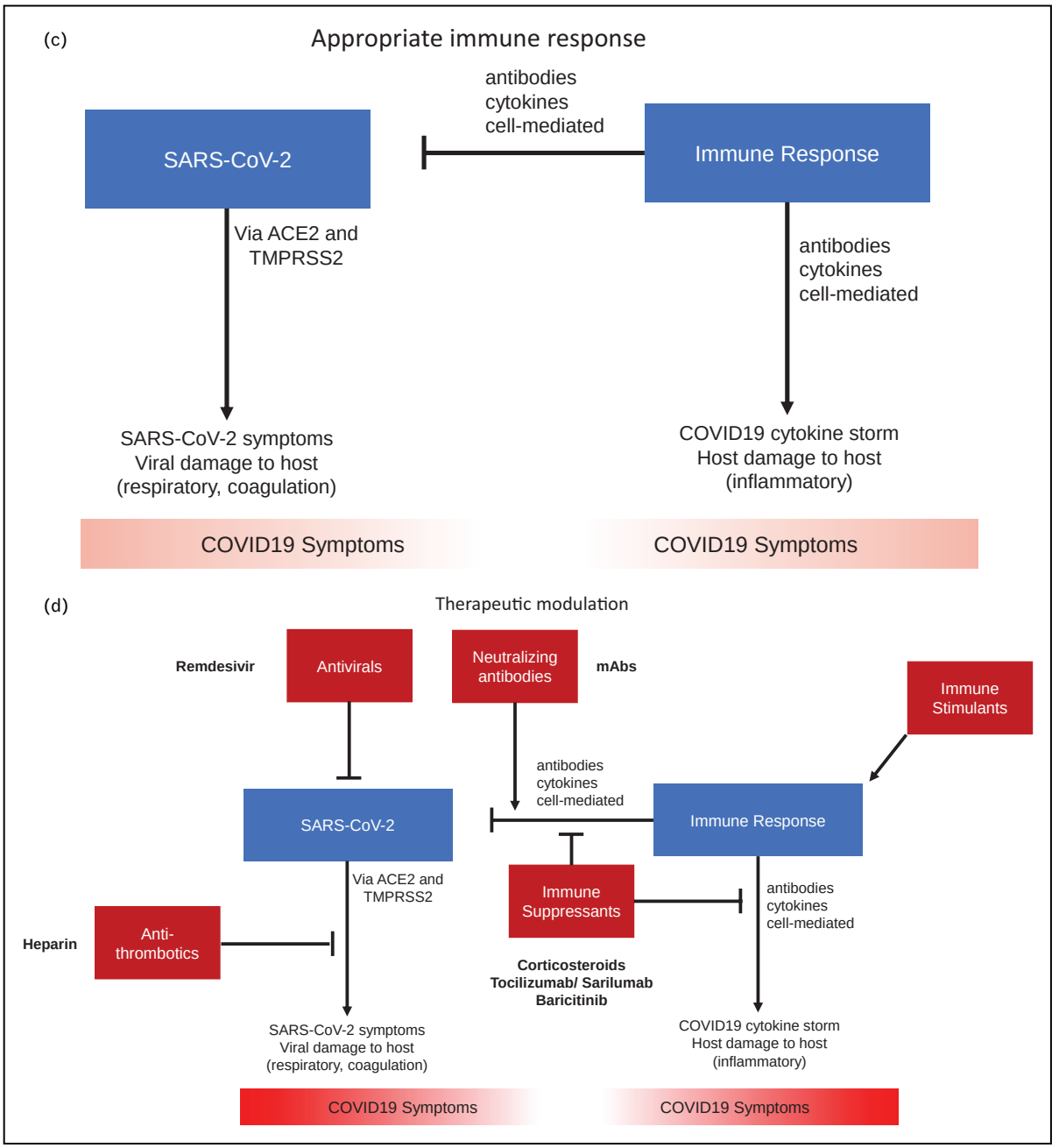

FIGURE 1. Continued.

extracorporeal membrane oxygenation (ECMO) in a small randomized controlled trial, though the timing of initiation and removal of anti-inflammatory and other regulatory factors may have contributed to worsening outcomes [20].

It is important to remember that circulating cytokine levels can be difficult to measure because cytokines have short half-lives, systemic levels may not accurately reflect local microenvironment, tissue concentrations (e.g. the pulmonary compartment), and measurements may not be easily obtained worldwide in real-time, due to the high costs and slow turn-around time for results [21▪].

HYPERINFLAMMATION IN COVID-19

Critically ill patients with COVID-19 often demonstrate features suggestive of cytokine storm, including fever, raised inflammatory markers and ARDS. However, the hyperinflammatory response in severe COVID-19 appears to be a unique and distinct entity and typically does not meet the classification criteria developed for MAS or HLH. The HScore (which generates a probability for the presence of HLH [22]) has poor diagnostic utility in COVID-19-cytokine storm [23–25]. Although ferritin levels predict mortality in COVID-19 [4], ranges are lower than those reported in patients with secondary HLH, and the

clinical syndrome in severe COVID-19 is lung-dominant without splenomegaly, typically without hypofibrinogenaemia, substantial derangements in liver function or cytopenias [26]. Of note, lymphopenia is almost universal in patients with severe COVID-19 [27], but the lymphocyte lineage is not classically affected in secondary HLH. In the context of COVID-19, therefore, lymphopenia might be the outcome of a viral driver or due to lung infiltration. Bone marrow haemophagocytosis, which is often reported in HLH, has also been seen in nonsurvivors of COVID-19 but it is unclear as to whether the haemophagocytosis should be expected in the context of critical illness or directly attributable to a hyperinflammatory state.

Several observational studies have aimed to develop criteria to identify a hyperinflammatory endotype associated with poor outcome in COVID-19. The currently published scoring systems include the validated Temple [28▪], COVID-19-associated hyperinflammatory syndrome (cHIS) [29▪], and COVID-19-associated hyperinflammation (COV-HI) criteria [30▪]. They differ in complexity and the number and thresholds of laboratory indices employed (Table 1). The Temple criteria used univariate logistic regression to identify variables associated with COVID-CS and then principal components analysis to find predictors that clustered together, followed by an iterative computational algorithm to define optimal cut-off values [28▪]. Ferritin and CRP did not add predictive power but were included in the final criteria per expert preference. The final model included essential entry criteria of confirmed COVID-19, ground glass opacities on chest imaging (computed tomography [CT] or radiograph), ferritin > 250ng/mL and CRP > 4.6 mg/dL; and [3] one feature from each cluster: cluster I (low albumin, low lymphocytes, high neutrophils), and cluster II (elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), D-dimer, LDH, troponin I), and cluster 3 (low anion gap, high chloride, high potassium, high blood urea nitrogen: creatinine ratio). Of 513 inpatients, 173 met these criteria (34%) and demonstrated far less favourable outcomes – a greater length of hospital stay (15.1 vs 5.7 days) and higher mortality (28.8% vs 6.6%). Differences were even more marked in the validation cohort and may have been higher without the use of steroids.

Clinical criteria for cHIS includes a six criterion additive scale of fever, macrophage activation (hyperferritinaemia), haematological dysfunction (neutrophil to lymphocyte ratio), hepatic injury (lactate dehydrogenase or AST), coagulopathy (D-dimer), and cytokinaemia (CRP, IL-6, or triglycerides) [29▪]. In total, 161 (54%) of 299 patients met > 2 cHIS criteria during their hospital admission; these patients had an increased risk of mortality (odds ratio 1.6 [95% CI 1.2–2.1], $P = 0.0020$) and requirement of invasive mechanical ventilation (odds ratio 4.3 [3.0–6.0], $P < 0.0001$). The cHIS score also correlated with severity of oxygen requirement and risk for clinical deterioration. The COVID-19-associated hyperinflammation (COV-HI) criteria is a more simple score, based on measurement of C-reactive protein (≥150 mg/L, or a doubling in 24 h from > 50 mg/L) and ferritin (>1500 μg/L) [30▪]. In total, 90 of 269 (33%) patients met the COV-HI criteria at admission. Despite having a younger median age and fewer comorbidities, patients with this phenotype had higher mortality (36 [40%] of 90 patients) than patients without the phenotype (46 [26%] of 179) during the 28-day follow-up period, and meeting the criteria was associated with an increased next-day risk of death or need for escalated respiratory support (combined endpoint; hazard ratio 2.24 [95% CI 1.62–2.87]), after adjustment for age, sex and comorbidity.

Taken together these studies demonstrate existence of subgroups of COVID-19 patients exhibiting hyperinflammation that are associated with poor outcomes ([28▪,29▪,30▪], however the criteria used to define hyperinflammation are widely variable, e.g., the ferritin thresholds range from 250 to 1500 ng/mL (Table 1) and the Temple criteria includes markers of inflammation, systemic cell death, multiorgan tissue damage and electrolyte imbalance, whereas the COV-HI criteria focus only on inflammatory markers. The definitions of hyperinflammation were somewhat arbitrarily defined by either expert consensus [28▪,30▪], or literature review [29▪], which was limited by the paucity of data available at the time, potentially introducing confirmation bias. The vast majority of patients in the Temple cohort received steroids, which makes indirect comparisons of prevalence and outcomes difficult. Independent validation of these criteria in other cohorts is necessary, however will be challenging given that standard of care definitions have changed over time, by virtue of the accrual of clinical experience, improved supportive care and advances in background therapies (widespread use of dexamethasone and IL-6 blockade). Interestingly a recent report demonstrated that patients with systemic rheumatic disease hospitalised with COVID-19 had increased risk for hyperinflammation compared with matched comparators [31]. The cHIS criteria identified patients with hyperinflammation associated with poor outcomes in both patients with systemic rheumatic disease and comparators [31].

Table 1. Classification criteria for COVID-cytokine storm

	Temple [28▪]	cHIS [29▪]	COV-HI [30▪]
Sample size (*n*)			
Derivation cohort	513	299	269
Validation cohort	Yes (258)	Yes	No
Clinical/Imaging			
Fever	–	>38 °C	–
Ground-glass opacities chest imaging	CT (or X-ray)*	–	–
Laboratory			
Ferritin (ng/mL)	>250*	700	>1500
CRP (mg/L)	>46*	≥150	>150
IL-6 (pg/mL)	–	≥15	–
Triglyceride (mg/dL)	–	≥150	–
Neutrophil: lymphocyte ratio	–	≥10	–
Hb (g/dL)	–	≤9.2	–
Platelets ($\times 10^9$ cells/L)	–	≤110	–
d-dimer (μg/ml)	>4.9	≥1.5	–
LDH (U/L)	>416	≥400	–
Aspartate transaminase (AST) (U/L)	>87	≥100	–
Alanine transaminase (ALT) (U/L)	>60		–
Troponin I (ng/mL)	>1.09	–	–
Albumin (g/dl)	<2.8	–	–
Lymphocytes (%)	<10.2	–	–
Neutrophil Abs (K/mm^3)	>11.4	–	–
Anion gap (nmol/L)	<6.8	–	–
Chloride (nmol/L)	>106	–	–
Potassium (nmol/L)	>4.9	–	–
Blood urea nitrogen: creatinine ratio	>29	–	–
Fulfilment of criteria			
Interpretation:	*Entry criteria (orange) ground glass opacities on CT chest (or radiograph) AND elevated ferritin and CRP) with ≥1 variable from each of 3 clusters: cluster 1 (low albumin, low lymphocytes, high neutrophils); cluster 2 (elevated alanine aminotransferase, aspartate aminotransferase, D-dimer, LDH, troponin I); cluster 3 (low anion gap, high chloride, high potassium, high blood urea nitrogen:creatinine ratio).	≥2 from 6 criteria encompassing fever, macrophage activation, haematological dysfunction, coagulopathy, hepatic injury and cytokinaemia (including CRP concentration)	≥1 of CRP > 150 mg/L (or daily doubling from > 50 mg/L) or Ferritin > 1500 μg/L

cHIS, COVID-19-associated hyperinflammatory syndrome; CT, computed tomography.
Table showing three studies aiming to define subgroups of COVID-19 patients with associated cytokine storm/hyperinflammation and worsening outcomes, including essential (asterix) and possible (bold) criteria. The Temple criteria includes essential criteria (ground glass opacities on chest imaging, elevated ferritin and CRP) with one or more of the following criteria from three clusters. Cluster 1 (low albumin, low lymphocytes, high neutrophils); cluster 2 (elevated alanine aminotransferase, aspartate aminotransferase, D-dimer, LDH, troponin I); cluster 3 (low anion gap, high chloride, high potassium, high blood urea nitrogen:creatinine ratio). The cHIS criteria requires at least two of 6 criteria encompassing fever, macrophage activation, haematological dysfunction, coagulopathy, hepatic injury and cytokinaemia (including CRP concentration). The COV-HI criteria requires either an elevated CRP or ferritin.

IMMUNOMODULATORY TREATMENT IN COVID-19

Improvement in COVID-19 outcomes with selective cytokine blockade and immunosuppressive agents further supports the pathologic role of excessive cytokines and the existence of a cytokine storm in a portion of patients. However, lack of treatment response does not always refute a cytokine storm, because the efficacy of treatments is likely to depend on a number of factors including patient selection, dosing, and timing of intervention, as illustrated by the swinging pendulum of 'positive' and 'negative' efficacy trials of IL-6 blockade in COVID-19 [32]. Further support for this concept comes from trends towards worsening outcomes with administration of dexamethasone too early in the disease course [33] as well as administration of intravenous interferon beta-1a late in the disease course [34].

Corticosteroids and IL-6 blockade (tocilizumab or sarilumab; not formally approved for use in COVID-19) are now standard of care in patients with severe COVID-19 and JAK1/2 inhibition with baricitinib has emergency use authorization in the United States based on randomized controlled trials, supporting the concept of COVID-19 cytokine storm. However, the therapeutic implications of elevated inflammatory markers are unknown and posthoc subgroup analyses of these large trials are eagerly anticipated. It is tempting to speculate prediction of treatment response may be possible using criteria for COVID-hyperinflammation. An observational study suggested that patients with COVID-19 have a good response to glucocorticoids when the CRP level is high but a poor response when the level is low [35]. However, the prespecified CRP subgroup analysis in the REMAP-CAP trial, suggested a similar effect across all CRP terciles and did not support a differential treatment effect of IL-6 blockade by baseline CRP levels, compared with the placebo arm [36].

Whilst corticosteroids undoubtedly reduce mortality in severe COVID-19, it is intriguing that the doses required (6 mg daily dexamethasone dosage equivalent to approximately 40 mg oral prednisolone) are far lower than the doses usually required for cytokine storm, suggesting that the hyperinflammatory component of severe COVID-19 is different from other cytokine storms or that further benefit could be gained with increased dosing. An 86-patient randomized controlled trial found that a weight-adjusted course of methylprednisolone (2 mg/kg/day) was superior to the relatively lower 6 mg/day of dexamethasone [37]. The suggestion of potential harm with corticosteroids in patients not requiring supplemental oxygen [38] and an optimal 'window of opportunity' for inhibiting IL-6 [32] (in addition to corticosteroids) suggests that combination immunomodulation may be of benefit at a late stage in patients with severe disease. This is consistent with the widely accepted biphasic model of COVID-19 with an initial viraemic phase followed by hyperinflammatory phase, in which immunostimulation that enhances antiviral activity is helpful early (and probably harmful late) in the disease course, whereas immunosuppression is helpful late and harmful early [13▪▪]. In keeping with this theory, publications related to nebulised interferon-beta [39] and not yet published reports about inhaled or recombinant GM-CSF suggest they may be of benefit, especially early in the disease, whereas blockade with monoclonal antibodies directed against GM-CSF (targeting the ligand or its receptor) may be beneficial late in the disease course [40▪].

OTHER MECHANISMS INFLUENCING SEVERITY IN COVID-19

Although SARS-CoV-2 infections in children are generally mild and nonfatal, a paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), also known as multisystem inflammatory syndrome in children (MIS-C) or paediatric multisystem inflammatory syndrome can lead to serious illness and long-term side-effects. Pathophysiology of MIS-C/PIMS-TS is still unclear and possible mechanisms include antibody or T-cell recognition of self-antigens (viral molecular mimicry of the host) resulting in autoantibodies, antibody or T-cell recognition of viral antigens expressed on infected cells, formation of immune complexes which induce inflammation, and viral superantigen sequences which activate host immune cells [41]. Patients with MIS-C/PIMS-TS are effectively treated with immunomodulatory therapies, such as intravenous immunoglobulin, glucocorticoids and therapeutic blockade of IL-1 and IL-6. Patients with MIS-C/PIMS-TS meet the criteria of cytokine storm, however this is a very distinct hyperinflammatory disorder from severe COVID-19.

ARDS is a leading cause of mortality in COVID-19. In patients with ARDS from any cause, two distinct phenotypes have already been defined that can be identified using a model involving clinical and biomarker parameters [42]: a hyperinflammatory phenotype (characterised by elevated proinflammatory cytokines, increased incidence of shock, and higher mortality) [43] and a hypoinflammatory phenotype [44]. Using this model, the hyperinflammatory subphenotype of ARDS was less prevalent in patients with COVID-19 ARDS, compared with non-COVID ARDS [45]. In patients with COVID-19 ARDS, the mortality was higher in

patients with the hyperinflammatory subphenotype (63%) compared with the hypoinflammatory subphenotype (39%) [45]. Although this pattern was expected, the mortality in both groups overall was higher than expected when compared with non-COVID ARDS data, suggesting that there may be additional factors in COVID-19 accounting for high mortality, other than a cytokine storm alone, but also suggesting that a cytokine storm is unlikely to be specific only to COVID-19, and the host hyperinflammatory response is influential in ARDS from other causes as well. However, it is important to remember that the vast majority of cytokine-directed or immunosuppressive agents have failed to demonstrate an effect in non-COVID ARDS, so this may not be a clinically relevant comparison or may demonstrate the need for stratified and precision medicine approaches in non-COVID ARDS in order to target the subphenotype most likely to benefit [46]

Coexisting conditions such as hypertension, diabetes, and obesity are associated with more severe cases of COVID-19, possibly because of the preexisting chronic inflammatory state or a lower threshold for the development of organ dysfunction from the immune response [13▪▪]. Other host factors, including genetic variation may also impact COVID-19 severity. IFN down-regulation may increase vulnerability to viral infections and autoantibodies against IFN may dampen the host antiviral response to prevent damage from pathogen-induced inflammation. Genome-wide association in 2,444 patients with COVID-19 identified polymorphisms associated with critical illness, including interferon (IFN) pathway genes IFNAR2 and OAS1/2/3, suggesting increased susceptibly to viral infections and impaired host defence [47]. Mutations in genes involved in the regulation of type I and III IFN immunity were enriched in patients with severe COVID-19, using a candidate gene approach [48]. The importance of interferons in the immune response against COVID-19 is also reflected in the striking finding of autoantibodies against type I interferons (mostly against IFN-α2 and IFN-ω, largely showing neutralising capacity *in vitro*) in 135 (13.7%) of 987 patients with life-threatening COVID-19 [49▪]. These antibodies were only detected in 4 (0.3%) of 1227 unexposed, healthy individuals [49▪]. Additionally, single-cell transcriptional profiling revealed profound suppression of interferon signalling among patients with COVID-19 compared with seasonal influenza [15]. Finally, a recent study found that interferon-stimulated gene expressing cells were systemically absent in patients with severe COVID-19 compared to mild disease [50]. Paradoxically, patients with severe COVID-19 produced very high levels of anti-SARS-CoV-2 antibodies and had a lower viral load, but they also produced antibodies that functionally blocked the production of the ISG-expressing cells associated with mild disease. Another study that screened 194 patients with COVID-19 for autoantibodies against 2,770 extracellular and secreted proteins (members of the exoproteome) found that COVID-19 patients exhibited marked increases in autoantibody reactivities, particularly immunomodulatory proteins (including cytokines, chemokines, complement components and cell-surface proteins) as compared to uninfected individuals [51]. Interestingly murine surrogates of these autoantibodies increased disease severity in a mouse model of SARS-CoV-2 infection [51]. These autoantibodies likely contribute to pathogenesis through a variety of mechanisms including impairing virological control by inhibiting immunoreceptor signalling and stimulating antibody-mediated inflammation. Thus, efforts to eliminate pathological autoantibodies may be a promising approach to prevent severe COVID-19

CONCLUSION AND FUTURE DIRECTIONS

The pathomechanistic hypothesis of COVID-19 involving a cytokine storm has stimulated an extraordinary degree of thinking, discussion and research. The term 'cytokine storm' has provoked some controversy, given the lack of clear definition until recently. It is now widely accepted that in a subgroup of patients with severe COVID-19 there is an exuberant inflammatory response, triggered by an initial viral insult, resulting in significant secondary organ dysfunction that can be averted in a portion of patients with targeted anti-cytokine or immunosuppressive therapies. Severe COVID-19 is likely to reside under the cytokine storm umbrella, possibly as a distinct entity. It is now clear that the host inflammatory responses contributing to lung injury in COVID-19 are complex and that conventional criteria (e.g. the H-score) for classical, established cytokine storm syndromes like HLH/MAS perform poorly to identify COVID-19-associated hyperinflammation. In Table 2, we present the evidence for and against severe COVID-19 involving a cytokine storm.

Patients with severe COVID-19 have a distinct immunopathology that resembles hyperinflammation. Using single parameter thresholds (e.g. IL-6 or CRP alone) or response to immunomodulation to confirm or refute the presence of cytokine storm is perhaps too reductionistic. Accumulating data will hopefully enable the generation of multivariate, composite prognostic models, incorporating routinely

Table 2. Evidence for and against severe COVID-19 involving a cytokine storm

	FOR	AGAINST
Cytokine levels	Cytokine levels (e.g IL-6, GM-CSF) are elevated in severe COVID-19 and increasing levels are strongly associated with worsening outcomes There are increased frequencies of circulating activated CD4+ and CD8+ T cells and plasmablasts in severe COVID-19	The elevated cytokines and activated immune cells in severe COVID-19 may be necessary for controlling SARS-CoV-2 infection The levels of several cytokines are only modestly elevated in COVID-19, relative to ARDS, sepsis, CART-CRS, and influenza
Clinical and Laboratory features	Clinical and lab abnormalities, such as elevated CRP and d-dimer levels, hypoalbuminemia, renal dysfunction, and effusions, are observed in COVID-19, as they are in other cytokine storms	These clinical and laboratory abnormalities can appear in an appropriate robust immune response to a pathogen Lymphopenia is not often found in cytokine storm disorders, but it is a hallmark of severe COVID-19
Classification criteria	Severe COVID-19 patients demonstrate all three features of cytokine storm (13): elevated circulating cytokines, acute inflammatory symptoms, and organ dysfunction secondary to hyperinflammation New classification criteria have been proposed that are associated with hyperinflammation and worsening outcomes: Temple (28), COVID-19-associated hyperinflammatory syndrome (cHIS)(29), and COVID-19-associated hyperinflammation (COV-HI) (30)	Conventional criteria for cytokine storm observed in HLH perform poorly in COVID-19 (e.g. H score)
Treatment	Immunomodulation (Corticosteroids and IL-6 inhibition) can reduce mortality in severe COVID-19, suggesting that excess inflammation is a modifiable pathogenic component of severe COVID-19 Additional immunomodulators including JAK1/2 inhibitors have demonstrated a potential role in severe COVID-19	Cytokine removal with CytoSorb led to worsening outcomes in critically ill patients on extracorporeal membrane oxygenation (ECMO)
Other host factors	Increased SARS-CoV-2 specific antibodies and decreased viral loads are found in patients with severe COVID-19 Longitudinal immunological correlates of disease outcomes have demonstrated distinct signatures of 'immunological misfiring' in COVID-19	Other host factors also have significant contribution to poor outcomes in severe COVID-19, including chronic illness comorbidities, thromboembolic events, genetic polymorphisms and auto-autoantibodies directed against interferons and other proteins.

SARS-CoV-2, severe acute respiratory coronavirus 2.

available biomarkers (e.g. CRP) with clinical variables (e.g. oxygen saturations) and cytokine/chemokine panels (e.g. IL-6, CXCL-9) to enable prognostic scoring and identification of optimal treatment approaches with strong predictions of response [52]. There has been some progress in prognostic biomarker discovery from the first wave of the pandemic, but attention now needs to turn to predictive biomarkers, with the advent of more immunomodulatory treatment options on the horizon (e.g. janus kinase inhibition). Soluble urokinase plasminogen activator receptor (suPAR) is emerging as a potential candidate companion biomarker to predict responses to IL-1 receptor antagonism with anakinra (not formally approved for COVID-19, but used in HLH [53▪]) in COVID-19 [54].

The beneficial effect of corticosteroids [33,55], IL-6 receptor antagonists [36], and recent reports with JAK inhibition (tofacitinib, JAK1/3 inhibitor, not formally approved for COVID-19 [56]) suggest that inflammation is a modifiable component of COVID-19 pathogenesis. However, there is spectrum of clinical phenotypes with differential responses to immunomodulatory therapy. The pattern, severity and mechanism of the hyperinflammatory state in COVID-19 and influence on endothelial activation and the hypercoagulable state and thrombotic outcomes is still unclear [57], as is the potential impact of hyperinflammation in the acute phase on complications in the convalescent phase, during which patients may have persistent symptoms ('long-COVID' or 'post-COVID syndrome'). It is unclear if the widescale use of immunomodulation in the acute phase and roll-out of COVID-19 vaccination will modulate the occurrence or presentation of hyperinflammation in COVID-19.

During a rapidly evolving global pandemic, it is important to maintain measured clinical and scientific equipoise. Hypotheses and research questions are intended to stimulate and refine thinking and research. The concept of COVID-19 cytokine storms or hyperinflammation is now widely accepted, a hypothesis proposed during the early data-deprived stage of the pandemic. However, despite the

considerable progress at rapid pace, there still remain multiple unknowns and continuing data collection and bioregistries are imperative.

COVID-19 has brought global attention to the concept of cytokine storms. Although there has been progress in understanding the mechanistic basis for the imitation and propagation of cytokine storm syndromes, there remains a considerable unmet need for effective therapies. We are continuing to advance the CORONA Project (www.CDCN.org/CORONA) to identify and advance the most promising treatments for COVID-19. Better understanding of the aetiopathogenesis, and identification of biomarkers to predict treatment response and prognosis, will hopefully enable a stratified and ultimately precision medicine treatment approach.

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Conflicts of interest

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The role of immunomodulatory medications in the treatment of COVID-19

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Purpose of review
Given the role of inflammation in severe forms of COVID-19, glucocorticoids and disease-modifying antirheumatic drugs (DMARDs) have been assessed as potential COVID-19 therapies.

Recent findings
Randomized controlled trials (RCTs) have shown that glucocorticoids reduce mortality in severe COVID-19. RCTs of DMARDs have shown mixed results varying on intervention and inclusion criteria. DMARDs, including colchicine or biologic agents, may improve COVID-19 outcomes in specific patient populations.

Summary
Glucocorticoids are an effective treatment for the management of severe COVID-19. Further studies are needed to better define the patient populations who could benefit from DMARD use, as well as provide guidance regarding the timing of these interventions.

Keywords
COVID-19, disease-modifying antirheumatic drugs, glucocorticoids, hyperinflammatory

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory coronavirus (SARS-CoV-2), has led to an unprecedented global health crisis with over 170 million confirmed cases and over 3.7 million deaths as of June 2021 [1]. The severe forms of COVID-19, a hyperinflammatory syndrome characterized by lymphopenia and elevated transaminases, lactate dehydrogenase (LDH), ferritin, D-dimers, as well as elevated inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), tumor-necrosis factor (TNF)-α and IL-8 have been described [2,3▪,4]. Some of these features have been identified as poor prognostic factors in patients with COVID-19, independent of other well-established risk factors such as older age, male sex, obesity, and increased comorbidity burden.

Given the resemblance to other hyperinflammatory conditions such as macrophage activation syndrome (MAS), also known as secondary hemophagocytic lymphohistiocytosis (HLH), or chimeric antigen receptor (CAR) T-cell induced cytokine release syndrome (CRS), several immunosuppressive therapies have been and are currently being investigated for the treatment of severe COVID-19. The aim of this review is to summarize data, primarily from randomized clinical trials, regarding the use of immunosuppressive treatments, including glucocorticoids, and disease-modifying antirheumatic drugs (DMARDs) for the treatment of COVID-19 up to May 30th, 2021.

RATIONALES FOR USE OF IMMUNOMODULATORS IN COVID-19

Infection of cells expressing angiotensin-converting enzyme 2 receptors by SARS-CoV-2 represents the initial phase of the disease [5]. The later stage, which is characterized by increased production of proinflammatory cytokines and chemokines such as IL-1, IL-6, TNF-α, and IL-8, mediates organ damage and failure leading to death in severe COVID-19 [6▪,7]. It is important to note that this two-phase approach is simplistic and that these processes occur concomitantly, resulting in infection of endothelial cells,

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KEY POINTS

- In patients with COVID-19 infection and oxygen requirements, glucocorticoids are associated with improved outcomes including mortality.
- Most recent randomized trials using IL-6 inhibitors have shown improvement in outcomes in patients with severe COVID-19 infection.
- Further studies are needed to clarify the role of other DMARDs for the treatment of COVID-19, including the specific patient populations that would benefit from such interventions.

both micro- and macrovascular thrombosis, tissue hypoxia, and cellular death [8].

Although DMARDs are predicted to minimize the hyperinflammation, Janus kinase (JAK) inhibitors could additionally have a role in the inhibition of viral entry by blocking AP2-associated protein kinase 1 (AAK1), a regulator of the endocytosis [9].

CLINICAL PHENOTYPE AND INCLUSION CRITERIA

The initial therapeutic approach to COVID-19 hyperinflammatory state was based on previous experiences with other hyperinflammatory syndromes such as MAS/HLH. However, recent studies comparing characteristics between these two conditions have highlighted some differences. Compared to MAS/HLH, which is characterized by activation of an IL-18-interferon-γ axis, COVID-19 hyperinflammatory state is characterized by elevation of IL-1 receptor antagonist, intracellular adhesion molecule 1, and IL-8, as well as reduced levels of soluble Fas ligand [10]. Also, a study evaluating patients with COVID-19 hyperinflammation showed that they did not fulfill MAS/HLH classification criteria such as the HScore and 2004-HLH diagnostic criteria, despite having evident hyperinflammation features [11].

Two different sets of criteria for COVID-19 hyperinflammatory states have been proposed and validated (Table 1) [12▪▪,13▪▪]. In both studies, criteria identified patients at increased risk of prolonged hospitalization, mechanical ventilation, or death. Further studies are needed to better understand the ability of these criteria to discriminate potential benefits of anti-inflammatory therapy. Recently, these criteria have shown an association with hyperinflammation and worse outcomes in patients with rheumatic diseases [14▪].

ANTIRHEUMATIC DRUGS FOR COVID-19

Glucocorticoids

Given the lack of benefits of glucocorticoids in infection-associated syndromes such as influenza, septic shock, and acute respiratory distress syndrome (ARDS), there was significant hesitancy regarding their use in patients with SARS-CoV-2 infection [15]. However, glucocorticoids were used from very early in the pandemic and observational studies showed mixed results [16].

Beneficial effects of dexamethasone for the treatment of severe COVID-19 were initially shown by the RECOVERY trial [17▪]. In this open-label

Table 1. Proposed criteria for COVID-19 hyperinflammatory syndrome

Temple COVID-19 Cytokine Storm Criteria Caricchio *et al.* [12▪▪]	**COVID-19-associated hyperinflammatory syndrome (CHIS) Webb *et al.* [13▪▪]**
Signs/symptoms of COVID-19	Fever > 38°C
RT-PCR for COVID-19	
Ground-glass opacity by HRCT or chest X-ray	
Ferritin > 250 ng/ml	Ferritin ≥ 700 ug/L
CRP > 4.6 mg/dl	IL-6 ≥15 pg/mL, or triglyceride ≥ 150 mg/dL, or CRP ≥ 15 mg/dL
Cluster 1 (one of the following): albumin < 2.8 g/dl, lymphocytes (%) <10.2, neutrophil (absolute) > 11.4 K/mm^3	Neutrophil to lymphocyte ratio ≥ 10, or both hemoglobin ≤ 9.2 g/dL and platelet count ≤ 110 × 10^9 per L
Cluster 2 (one of the following): ALT > 60 U/L, AST > 87 U/L, D-dimer > 4,930 ng/ml, LDH > 416 U/L, Troponin I > 1.09 ng/ml	LDH ≥ 400 U/L or AST ≥ 100 U/L
Cluster 3 (one of the following): Anion gap < 6.8 mmol/L, chloride > 106 mmol/L, potassium >4.9 mmol/L, BUN:creatinine ratio > 29	D-dimer ≥ 1.5 ug/mL

RT-PCR, real time polymerase chain reaction; HRCT, high-resolution chest tomography; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; IL-6, interleukin-6.

adaptive platform randomized controlled trial (RCT), dexamethasone 6 mg (PO or IV) daily for up to 10 days was shown to decrease mortality at 28 days (age-adjusted RR 0.83 [95% CI 0.74–0.92]) when compared to standard of care (SOC). This benefit was observed among patients who required mechanical ventilation (age-adjusted rate ratio (RR) 0.64 [95% CI 0.51–0.91]) or supplemental oxygen (age-adjusted RR 0.82 [95% CI 0.72–0.94]), but showed no benefit, and even concern for possible harm, among patients who did not require respiratory support (age-adjusted RR 1.19 [95% CI 0.91–1.55]). Since the release of RECOVERY, which led to changes in the treatment protocols for patients with COVID-19, several other studies have confirmed these findings using either different formulations (e.g., hydrocortisone, methylprednisolone) or dosing protocols (Table 2) [18–22]. A recent systematic review and meta-analysis of glucocorticoid treatment in COVID-19 showed a benefit of decreased mortality (odds ratio (OR) 0.66 [95% CI 0.52–0.82]) among all patients [23▪].

It is important to note that despite this encouraging data, registry studies of patients with autoimmune disease and baseline glucocorticoid use have shown an increased risk of severe COVID-19 with higher doses of glucocorticoids. Data from the COVID-19 Global Rheumatology Alliance (GRA) showed increased risks of both hospitalization and death in patients with baseline prednisone doses of 10 mg or higher [24,25▪▪]. Limitations to these registries, such as confounding by indication, limit the ability to fully disentangle these associations. However, these data, especially in conjunction with the RECOVERY findings in patients not on ventilatory support, may suggest that timing of intervention might be critical and that use of glucocorticoids could have a different effect depending on the phase of the disease.

Colchicine

Due to its ability to inhibit the NLRP3 inflammasome, leading to suppression of IL-1β, IL-18, and IL-6, colchicine has been proposed as a potential therapeutic for noncritically ill patients with COVID-19 [26]. An Italian cohort study using historical comparators receiving SOC, showed that patients treated with colchicine had a lower risk of death (hazard ratio (HR) 0.15 [95% CI 0.06–0.37]) [27]. Similar results were observed in another Italian single-center propensity score-matched cohort study, showing improving odds of discharge at day 28 and decreased overall mortality (9.1% vs 33.3%, OR 0.20 [95% CI 0.05–0.80]) [28].

An initial open-label RCT from Greece, the Greek Effects of Colchicine in COVID-19 (GRECCO-19) trial, compared colchicine vs SOC in 105 hospitalized COVID-19 patients [29]. The primary outcome, time to deterioration by 2 points in World Health Organization-Clinical Progression Scale (WHO-CPS), was longer in the colchicine arm compared to SOC (20.7 days vs 18.6 days, $P = 0.03$). No difference was observed in the other primary endpoints, including peak high-sensitivity troponin or resolution of CRP levels. Note that more clinically relevant outcomes would have been 30 and 60-day survival as the course of the disease was very heterogeneous and none of these parameters helped predict those at high risk of dying. Most recently, results from the Colchicine for community-treated patients with COVID-19 (COLCORONA) trial, were published [30▪]. In this multicenter RCT of 4488 patients with suspected or confirmed COVID-19 diagnosis, colchicine was administered at a dose of 0.5 mg twice per day for 3 days and later 0.5 mg daily for 27 days vs placebo. In the primary composite outcomes of hospitalization or death, a nonstatistically significant difference was observed (4.7% vs 5.8%, OR 0.79 [95% CI 0.61–1.03]). However, in the prespecified subgroup analysis of 4159 patients with PCR-confirmed COVID-19, a significant decrease in the primary endpoint was observed in patients treated with colchicine (4.6% vs 6.0%, OR 0.75 [95% CI 0.57–0.99]). This yielded a number needed to treat (NNT) of 70 (95% CI 36–1842). Except for a higher incidence of pulmonary embolism in the treatment arm, there were no differences in serious adverse events. The trial was terminated early due to logistical issues therefore potentially underpowering the conclusions. Although its use in high-risk patients might be convenient due to simple route of administration, low cost and relatively safe profile, the potential benefit on mortality is still unclear and will be hopefully clarified by several ongoing trials.

Interleukin-6 inhibitors

The initial associations between IL-6 elevation and COVID-19 severity sparked interest in the use of IL-6 inhibitors for the treatment of severe COVID-19. Initial observational studies showed promising results, and a meta-analysis including 16 studies showed a decreased risk of death (pooled OR 0.57 [95% CI 0.36–0.92]) associated with the use of tocilizumab (TCZ) compared to SOC [31]. Significant heterogeneity among studies was noted. Importantly, several of these studies focused on specific selection criteria that included documented infection with respiratory failure and markers of inflammation (e.g., CRP, ferritin) [32].

Despite encouraging data from observational studies, early RCTs did not confirm these earlier

Table 2. Clinical trials assessing glucocorticoid treatment in patients with COVID-19

Study/Sites	Population	Inclusion Criteria	Intervention (dose, timing, duration)	Primary Endpoint	Results	Observations
RECOVERY Horby *et al.* [17▪] UK	Hospitalized patients	Suspected or confirmed SARS-CoV-2 infection	Dexamethasone (PO/IV) 6 mg daily up to 10 days ($n=2104$) vs SOC ($n=4321$)	28-day mortality	Reduced mortality with age-adjusted rate ratio 0.83 (95% CI 0.75 to 0.93)	Benefit observed only in patients requiring supplemental oxygen or mechanical ventilation
REMAP-CAP Angus *et al.* [18] North America, Europe, Australia	ICU patients	Suspected or confirmed SARS-CoV-2 infection and respiratory or cardiovascular organ support	IV Hydrocortisone fixed dose 50 mg or 100 mg q6h ($n=143$) vs shock-dependent course 50 mg q6h ($n=152$) vs SOC ($n=108$)	Organ support-free (alive and free of ICU-based respiratory or cardiovascular support) days at 21 days	Superiority in both intervention arms with median organ support-free days of 0 (IQR -1 to 15) vs 0 (IQR -1 to 13) vs 0 (IQR -1 to 11), respectively	Bayesian analysis showing 93% and 80% probability of superiority for fixed-dose and shock-dependent dose, respectively, compared to SOC. Study stopped early due to RECOVERY results
CAPE COVID Dequin *et al.* [20] France	ICU patients	Suspected or confirmed SARS-CoV-2 infection and respiratory failure with at least 1 ventilatory criteria	IV hydrocortisone continuous infusion 200 mg/d for 7 days, then tapered by day 14 ($n=76$) vs SOC ($n=73$)	Treatment failure at day 21, defined as death or persistent dependency on mechanical ventilation or high-flow oxygen	69 treatment failure events, 42.1% with hydrocortisone vs 50.7% with SOC (difference -8.6% [95% CI -24.9 to 7.7%])	Study stopped early by DSMB, pending RECOVERY results. No differences in secondary outcomes including intubation, pronation or use of ECMO
CODEX Tomazini *et al.* [22] Brazil	ICU patients	Suspected or confirmed SARS-CoV-2 infection on mechanical ventilation	IV dexamethasone 20 mg daily for 5 days, then 10 mg daily for 5 days ($n=151$) vs SOC ($n=148$)	MV free-days at day 28	Mean 6.6 ventilator-free days (95% CI 5.0–8.2) vs 4.0 ventilator-free days (95% CI 2.9–5.4) (difference -1.16, [95% CI -1.94 to -0.38)], respectively	No difference in secondary outcomes including all-cause mortality, or adverse events. Trial stopped early given RECOVERY results
GLUCOCOVID Corral-Gudino *et al.* [19] Spain	Hospitalized patients, non-ICU	Suspected or confirmed SARS-CoV-2 with symptoms for at least 7 days, X-ray evidence of pneumonia, abnormal gas exchange and evidence of systemic inflammatory response	IV methylprednisolone 40 mg BID for 3 days, then 20 mg BID for 3 days ($n=56$) vs SOC ($n=29$)	Composite outcomes of death, admission to ICU, or requirement of noninvasive ventilation	Relative risk 0.68 (95% CI, 0.37 to 1.26)	22 patients in the intervention arm were allocated by the treating physicians. 21 patients received other anti-inflammatory treatments

Table 2 (*Continued*)

Study/Sites	Population	Inclusion Criteria	Intervention (dose, timing, duration)	Primary Endpoint	Results	Observations
METCOVID Jeronimo *et al.* [72] Brazil	Hospitalized patients	Suspected SARS-CoV-2 infection and SpO2 ≤ 94% on room air OR under mechanical ventilation	IV methylprednisolone 0.5 mg/kg BID for 5 days ($n = 194$) vs SOC ($n = 199$)	28-day mortality	Deaths 37.1% with methylprednisolone vs 38.2% with SOC, HR 0.92 (95% CI 0.67 to 1.28)	Mortality reduced in subgroup analysis of patients > 60 years (HR 0.63 [95% CI 0.41–0.98])
Ranjbar *et al.* [21] Iran	Hospitalized patients	Confirmed SARS-CoV-2 infection and SpO2 < 92% on room air	IV methylprednisolone 2 mg/kg/d and tapering dose every 5 days ($n = 47$) or IV dexamethasone 6 mg/d for 10 days ($n = 46$)	28 day mortality and clinical status at days 5 and 10 (WHO ordinal scale)	23 deaths, 18.6% methylprednisolone vs 37.5% dexamethasone ($P = 0.08$)	For methylprednisolone treated patients, improved clinical status seen at days 5 and 10 ($P = 0.002$ and $P = 0.001$, respectively)

IV, intravenous; PO, oral; SOC, standard of care; ICU, intensive care unit; IQR, interquartile range; SpO2, oxygen saturation; DSMB, data safety monitoring board; CI, confidence interval; MV, mechanical ventilation; ECMO, extracorporeal membrane oxygenation; HR, hazard ratio; WHO, World Health Organization.

observations (Table 3). The CORIMUNO-19 and COVACTA trials, which did not include inflammatory criteria for inclusion, failed to meet their primary endpoints [33,34]. The RCT-TCZ-COVID-19 and BACC BAY trials, which did include inflammatory criteria for inclusion, were potentially underpowered due to early stoppage or an unexpected low number of events, respectively [35,36]. More recent and larger RCTs, where most patients enrolled were also receiving background glucocorticoid treatment, have shown more positive results with regards to the use of IL-6 inhibition in severe COVID-19. The EMPACTA trial, which included 389 patients, showed a 44% decreased risk (HR 0.56 [95% CI 0.33–0.97]) of the composite outcomes of mechanical ventilation or death associated with the use of TCZ [37]. No improvement in all-cause death was observed. In the REMAP-CAP trial, that randomized patients to either TCZ, sarilumab or placebo, an improvement in organ support-free days and increased survival at 90 days were seen for both IL-6 inhibitors [38▪].

These results have been also confirmed by more recent trials including the RECOVERY trial. In the TCZ intervention arm from the RECOVERY adaptive platform, where 4116 patients were randomized to either TCZ or SOC, the risk of all-cause death was lower in patients treated with TCZ (adjusted RR 0.85 [95% CI 0.76–0.94]) [39▪▪]. Decrease in time to discharge and composite of mechanical ventilation and death was also lower in the intervention arm. These new findings, therefore, suggest benefits from the use of IL-6 inhibition, in addition to background glucocorticoid treatment, in patients with elevated markers of inflammation.

Interleukin-1 inhibitors

Transcriptomic analysis of whole blood of COVID-19 patients showed increasing expression IL-1α and IL-1β prior to the nadir of respiratory function, unlike other proinflammatory cytokines [40]. Also, given the clinical similarities between cytokine storm syndromes and COVID-19 hyperinflammation, use of IL-1 inhibitors for the treatment of severe COVID-19 was considered early in the pandemic [41–44].

Early case series and cohort studies suggested improvement in clinical outcomes of severe COVID-19 with anakinra, an IL-1 receptor antagonist. In a meta-analysis of two large cohort studies, anakinra was associated with a lower risk of mortality (pooled HR 0.2 [95% CI 0.1–0.4]) [16]. Despite these encouraging results, RCTs have not supported these observations (Table 4). The CORIMUNO-ANA-1 trial, a French multicenter open-label study, randomized patients to intravenous anakinra (200 mg BID on days 1–3, 100 mg BID on day 4, and 100 mg once on day 5)

Table 3. Studies assessing Interleukin-6 inhibitor treatment in patients with COVID-19

Study/Sites	Design/Population	Inclusion Criteria	Intervention (dose, timing, duration)	Primary Endpoint	Results	Observations
SARI-RAF Della-Torre *et al.* [32] Italy	Open-label, not randomized/ Hospitalized	Confirmed SARS-CoV-2 infection with bilateral pneumonia with SpO2 $\leq$ 92% or PaFiO2 $\leq$ 300 mmHg and hyperinflammation (elevated LDH and one of the following: CRP $\geq$ 100 mg/l, IL-6 $\geq$ 40 pg/ml, ferritin $\geq$ 900 ng/ml)	SAR 400 mg once ($n=28$) vs SOC ($n=28$)	Clinical improvement (WHO-CPS) and mortality at 28 days	No difference in clinical improvement (61% vs 64%, $P=0.94$) or mortality (7% vs 18%, $P=0.21$)	Median time to clinical improvement shorter in sarilumab treated patients (10 days vs 24 days, $P=0.01$). SOC includes antiviral, hydroxychloroquine and antibiotic therapy.
CORIMUNO-19 Hermine *et al.* [33] France	Open-label RCT/ Hospitalized non-ICU patients	Confirmed SARS-CoV-2 with moderate, severe or critical pneumonia (O2 > 3L/min) (intubation excluded)	IV TCZ 8 mg/kg single dose ($n=64$) vs SOC ($n=67$). Option of second dose at 72h	Score > 5 on WHO-CPS at day 4 and intubation or death at day 14	No difference in WHO-CPS (ARD -9.0% [90 CrI -21.0 to 3.1]) On day 14, 24% with TCZ vs 36% with SOC (HR 0.58 [90% CrI 0.33–1.00])	No difference on intubation or death at day 28. 17% of patients with background glucocorticoids.
RCT-TCZ-COVID-19 Salvarani *et al.* [36] Italy	Open-label RCT/ Hospitalized non-ICU patients	Confirmed SARS-CoV-2 with PAFiO2 200–300 mmHg and inflammatory phenotype: fever (> 38°C) last 2 days and/ or CRP $\geq$ 10 mg/dL or CRP doubled since admission	IV TCZ 8 mg/kg single dose ($n=60$) vs SOC ($n=66$). Option of second dose at 12h	Composite outcome of clinical worsening including MV, death or PaFIO2 < 150 mmHg	28.3% with TCZ vs 27.0% in SOC (RR 1.05 [95% CI 0.59–1.86])	Stopped early due to futility on interim analysis.
BACC BAY Stone *et al.* [35] US	Double-blinded RCT/ Hospitalized non-ICU patients	Confirmed SARS-CoV-2 with at least 2 of the following: fever (> 38°C) within 72h of enrollment, pulmonary infiltrates, supplementary oxygen to maintain SpO2 $\geq$ 92%; and one of the following: CRP > 50 mg/L, ferritin > 500 ng/ml, D-dimer > 1000 ng/ml, LDH > 250 U/L	IV TCZ 8 mg/kg single dose ($n=161$) vs SOC ($n=82$)	MV or death (time-to-event)	17 events with TCZ vs 10 events in SOC (HR 0.83 [95% CI 0.38–1.81])	No benefit for secondary outcome of clinical worsening (HR 1.11 [95% CI 0.59–2.10) Possibly underpowered due to the low number of events.

Table 3 (*Continued*)

Study/Sites	Design/Population	Inclusion Criteria	Intervention (dose, timing, duration)	Primary Endpoint	Results	Observations
TOCIBRAS Veiga *et al.* [73] Brazil	Open-label RCT/ Hospitalized patients	Confirmed SARS-CoV-2 with supplemental oxygen or mechanical ventilation and at least two of the following: D-dimer > 1000 ng/ml, CRP > 5 mg/dl, ferritin > 300 ug/L, or LDG > ULN	IV TCZ 8 mg/kg single dose ($n=65$) vs SOC ($n=64$)	Clinical status (ordinal scale) at day 15	Patients on MV or deaths: 28% with TCZ vs 20% with SOC (OR 1.54 [95% CI 0.66–3.66])	No differences in 28 day or in-hospital mortality. 71% of patients on glucocorticoids.
EMPACTA Salama *et al.* [37] North and South America	Double-blinded RCT/ Hospitalized patients non-ICU	Confirmed SARS-CoV-2 receiving supplemental oxygen (noninvasive or invasive ventilation excluded)	IV TCZ 8 mg single dose ($n=259$) vs SOC ($n=128$). Option for second dose 8–24h	MV or death at day 28	12% with TCZ vs 19.3% with SOC (HR 0.56 [95% CI 0.33–0.97])	No improvement on death from any cause. Clinical failure assessed in time-to-event analysis favored TCZ. Majority of patients on glucocorticoids (>80%) and antiviral therapy (>70%).
COVACTA Rosas *et al.* [34] North America and Europe	Double -blind RCT/ Hospitalized patients	Confirmed SARS-CoV-2 with SpO2 $\leq$ 93% or PaFIO2 < 300 mmHg	IV TCZ 8 mg single dose ($n=301$) vs SOC ($n=151$). Option for second dose 8–24h	Clinical status (7-category ordinal scale) at day 28	Median value for clinical status on ordinal scale 1.0 with TCZ vs 2.0 with SOC (between group difference -1.0 [95% CI -2.5 to 0)	No difference in mortality at day 28. 37% on invasive MV at baseline.
REMAP-CAP Gordon *et al.* [38▪] Multiple countries	Open-label RCT/ICU patients	Suspected or confirmed SARS-CoV-2 on respiratory or cardiovascular organ support	IV TCZ 8 mg/kg single-dose ($n=353$) or IV SAR 400 mg ($n=48$) vs SOC ($n=402$)	Organ support-free days at day 21	Median number of organ support-free days 10 with TCZ (aOR 1.64 [95% CrI 1.25 to 2.14] for TCZ), 11 with SAR (aOR 1.76 [95% CrI 1.17–2.91]) vs 0 with SOC	Improved survival at 90 days for TCZ or SAR treated patients. > 80% of patients on glucocorticoids.

Table 3 (*Continued*)

Study/Sites	Design/Population	Inclusion Criteria	Intervention (dose, timing, duration)	Primary Endpoint	Results	Observations
Lescure *et al.* [74] Multiple countries	Double-blind RCT/ Hospitalized patients	Confirmed SARS-CoV-2 with severe (oxygen supplementation) or critical (noninvasive and invasive ventilation) disease	IV SAR 400 mg single dose ($n=173$) vs IV SAR 200 mg ($n=161$) vs SOC ($n=86$). Option for a second dose 24–48h	Time to clinical improvement of $\geq$ 2 points (7-category ordinal scale)	Median time to improvement 10 days with SAR 400 mg (HR 1.14 [95% CI 0.83–1.54]) vs 10 days with SAR 200 mg (HR 1.03 [95% CI 0.75–1.40]) vs 12 days with SOC	No difference in survival.
COVINTOC Soin *et al.* [75] India	Open-label RCT/ Hospitalized	Confirmed SARS-CoV-2 with moderate (RR 15–30/min and SpO2 90–94%) or severe (RR $>$ 30/min and SpO2 $<$ 90%) or ARDS or septic shock	IV TCZ 6 mg/kg ($n=90$) vs SOC ($n=90$). Option for second dose at 12h to 7d	Progression from moderate to severe, or severe to death up to day 14	Progression in 9% with TCZ vs 13% with SOC (mean difference -3.71 [95% CI -18.23 to 11.19])	91% of patients on glucocorticoids.
RECOVERY Abani *et al.* [39▪▪] UK	Open-label RCT/ Hospitalized patients	Suspected or confirmed SARS-CoV-2 with hypoxia (SpO2 $<$ 92%) and CRP $\geq$ 75 mg/L)	IV TCZ 400–800 mg ($n=2022$) vs SOC ($n=2094$)	All-cause death at day 28	31% with TCZ vs 35% with SOC (aRR 0.85 [95% CI 0.76–0.94])	Decrease in time to discharge and composite of MV or death (in non-MV patients at baseline). 80% patients on glucocorticoids.

IV, intravenous; SOC, standard of care; ICU, intensive care unit; IQR, interquartile range; SpO2, oxygen saturation; PaFIO2, ratio of arterial oxygen partial pressure to fractional inspired oxygen; TCZ, tocilizumab; SAR, sarilumab; CI, confidence interval; CrI, credible interval; HR, hazard ratio; OR, odds ratio; aRR, adjusted relative risk; WHO-CPS, World Health Organization Clinical Progression Scale; CRP, C reactive protein; LDH, lactate dehydrogenase; RR, respiratory rate; ARDS, acute respiratory distress syndrome.

Table 4. Studies assessing interleukin-1 inhibitor treatment in patients with COVID-19

Study/Sites	Design/ Population	Inclusion Criteria	Intervention (dose, timing, duration)	Primary Endpoint	Results	Observations
CORIMUNO-ANA-1 Bureau *et al.* [45▪▪] France	RCT/Hospitalized patients non-ICU	Confirmed SARS-CoV-2 infection with mild-moderate, severe or critical pneumonia and CRP > 25 mg/L	IV Anakinra 200 mg BID on day 1-3, then 100 mg BID day 4 and 100 mg day 5 ($n=59$) vs SOC ($n=57$) Additional doses given if no improvement after day 4	Score > 5 on WHO-CPS at day 4 or composite outcome of MV or death at day 14	WHO-CPS >5 at day 4: 36% with anakinra vs 38% with SOC (ARD -2.5% [90% CrI -17.1 to 12.0]) MV or death at day 14: 47% with anakinra vs 51% with SOC (HR 0.97 [90% CrI 0.62–1.52])	Study stopped early by recommendation of DSMB.
SAVE Kyriazopoulou *et al.* [47] Greece	Open-label nonrandomized with parallel controls/ Hospitalized patients non-ICU	Confirmed SARS-CoV-2 infection, imaging consistent with pneumonia and plasma suPAR levels > 6 ng/ml	SC anakinra 100 mg daily for 10 days ($n=130$) vs SOC ($n=179$)	Severe respiratory failure at day 14	22.3% with anakinra vs 59.2% with SOC (HR 0.30 [95% CI 0.20–0.46])	Parallel controls chosen by propensity-score matching. Decrease mortality.
OMA-COVID-19 Balkhair *et al.* [76] Oman	Prospective, open-label interventional study/ Hospitalized patients	Confirmed SARS-CoV-2 infection, imaging consistent with bilateral pneumonia, and at least one of the following: RR >30/min and SpO2 < 90% on RA, SpO2 ≤ 93% on oxygen ≥ 6L/ min, ARDS.	SC anakinra 100 mg BID for 3 days, then 100 mg daily for 7 days ($n=45$) vs SOC ($n=24$)	MV and in-hospital death	MV: 31% with anakinra vs 75% with SOC ($P<0.001$) In-hospital death: 29% with anakinra vs 46% SOC ($P=0.082$)	Historical controls. 60% on glucocorticoids.
CAN-COVID *Press release* [48] US and Europe	RCT/Hospitalized patients non-ICU	Confirmed SARS-CoV-2 infection, imaging consistent with pneumonia, SpO2 ≤ 93% on RA or PaFiO2 < 300 mmHg, and CRP ≥ 20 mg/L or ferritin ≥ 600 ug/L	Canakinumab weight-bases single dose vs SOC	Survival without MV at day 28	88% with canakinumab vs 85.7% with SOC ($P=0.29$)	No difference in mortality. Interim analysis, pending final publication.

IV, intravenous; SOC, standard of care; ICU, intensive care unit; SpO2, oxygen saturation; suPAR, soluble urokinase plasminogen activator receptor; CI, confidence interval; CrI, credible interval; HR, hazard ratio; OR, odds ratio; ARD, absolute risk difference; ARDS, acute respiratory distress syndrome; WHO-CPS, World Health Organization Clinical Progression Scale; CRP, C reactive protein.

or to SOC in patients with COVID-19 requiring at least 3L/min O_2 and a CRP greater than 25 mg/L [45▪▪]. The study was stopped early by recommendation of the data safety monitoring board, and no differences were found in the primary outcomes of improvement in clinical status at day 4 or need for mechanical ventilation or death at day 14. The Anakinra for COVID-19 Respiratory Symptoms (ANACONDA) study was also stopped early due to concern for worse outcomes in the intervention arm [46]. Results of this study are not available. Interestingly, a Greek open-label interventional study that allocated treatment with anakinra to patients with COVID-19 and elevated levels of soluble urokinase plasminogen activator receptor (suPAR) showed a decrease in mechanical ventilation in patients treated with anakinra [47].

Treatment with canakinumab, an IL- β inhibitor, has also been assessed in small case series and in larger studies. The CAN-COVID study, a phase 3 trial, randomized patients to either canakinumab or SOC [48]. Although results of the study have not been published, a press release in November 2020 announced that the study did not achieve its primary endpoint of improvement in survival without mechanical ventilation at day 28. Currently, the role of IL-1 inhibitors for the treatment of COVID-19 is not clear, and hopefully ongoing phase 3 clinical trials will better clarify this point.

Tumor necrosis factor α inhibitors

Based on observations of elevated TNF-α levels in patients with severe COVID-19, there is growing interest regarding the use of TNF-inhibitors for the treatment of COVID-19 [49]. In fact, a role for TNF inhibition in animal models of other viral lung diseases such as influenza has been proposed [50]. These mechanistic observations have also been reinforced by lower odds of severe COVID-19 in patients on baseline TNF-inhibitors such as rheumatic and inflammatory bowel disease patients [51▪]. Currently, five ongoing trials utilizing infliximab in hospitalized COVID-19 patients and one using adalimumab in ambulatory COVID-19 patients are ongoing (Table 5).

Table 5. Ongoing studies assessing tumor necrosis factor (TNF)-α inhibitor treatment in patients with COVID-19

Drug	Clinical Trials.gov Identifier	Design/Setting	Intervention	Inclusion criteria	Primary outcome
Infliximab	NCT04425538	Single group assignment/ hospitalized patients non-ICU	IV Infliximab 5 mg/kg. Option for second dose 7–21 days	Confirmed SARS-CoV-2 infection, pneumonia evidenced by imaging and at least one of the following: RR ≥ 30/min, SpO2 ≤ 93% on RA, PaFIO2 < 300, worsening lung involvement	Time to improvement in oxygenation
Infliximab	NCT04734678	Cohort/Hospitalized patients non-ICU	IV TCZ 400 mg single dose vs IV TCZ 400 mg single dose + IV Infliximab 5 mg/kg/d for 2 doses	Confirmed SARS-CoV-2 infection, pneumonia evidenced by imaging, hyperinflammation (either CRP ≥ 100 mg/L, ferritin ≥ 900 ng/ml with LDH > 220 U/L) and at least one of the following: RR ≥ 30/ min, SpO2 ≤ 93% on RA, PaFiO2 < 300, involvement	Clinical status improvement (6 category scale)
Infliximab ACTIV-1 IM	NCT04593940	RCT/Hospitalized patients	IV Infliximab 5 mg/kg single dose vs SOC	Confirmed SARS-CoV-2 infection with ongoing illness and at least one of the following: radiographic infiltrates, SpO2 ≤ 94% RA, supplemental oxygen requirement, MV or ECMO	Time to recovery by day 29
Infliximab RECOVERY	NCT04381936	RCT/Hospitalized	IV infliximab 5 mg/kg single dose vs SOC	Suspected or confirmed SARS-CoV-2 infection	All-cause mortality
Adalimumab COMBAAT	NCT04705844	RCT/ Nonhospitalized patients	SC Adalimumab 160 mg (40 mg, 4 doses) vs SOC	Confirmed SARS-CoV-2, COVID-19 related symptoms, SpO2 > 93%, and at least one of the following: CRP > 50 mg/L, lymphopenia < 1.5 x 10^9/L, neutrophilia > 7.5 x 10^9/L	Rate of progression to severe disease or death

IV, intravenous; SC, subcutaneous; SOC, standard of care; ICU, intensive care unit; SpO2, oxygen saturation; PaFIO2, ratio of arterial oxygen partial pressure to fractional inspired oxygen; TCZ, tocilizumab; CRP, C reactive protein; LDH, lactate dehydrogenase; RR, respiratory rate; MV, mechanical ventilation; ECMO, extracorporeal membrane oxygenation.

Janus kinase inhibitors

For the treatment of COVID-19 infection, JAK inhibitors have two proposed mechanisms of action: inhibition of viral entry to cells through disruption of AAK1 and decreased signaling of pro-inflammatory cytokines, such as IL-2, IL-6, and IFN-γ, through inhibition of the JAK-STAT pathway [9,52]. A meta-analysis of observational studies using baricitinib and ruxolitinib for the treatment of COVID-19 showed lower odds of mortality, ICU admission, and higher odds of discharge associated with treatment. It is important to note that studies included were observational and presented significant heterogeneity [53]. The Adaptive COVID-19 Treatment Trial 2 was the first published double-blind RCT comparing baricitinib against placebo (with background remdesivir) [54▪▪]. In this trial of 1033 hospitalized patients, those treated with baricitinib had a shorter time to recovery (7 vs 8 days, $P = 0.03$) and higher odds of clinical improvement (OR 1.3 [95% CI 1.0–1.6]). A nonsignificant trend toward lower mortality at day 28 was also noted. Most recently, the preprint results of a large global RCT of 1525 hospitalized patients showed no difference in its primary outcome of reduction of disease progression (OR 0.86 [95% CI 0.67–10.8]) [55]. However, a 38.2% reduction in mortality was observed in all prespecified groups. In both trials, no difference in venous thromboembolic events was noted.

Interestingly, similar to glucocorticoids, baseline use of JAK inhibitors has been associated with worse COVID-19 outcomes. A recent analysis of a large cohort of rheumatoid arthritis (RA) patients showed that use of JAK inhibitors was associated with a higher risk of worse COVID-19 severity (OR 1.52 [95% CI 1.02–2.28]) compared to TNF inhibitors [56▪]. These findings may be associated with inhibition of the interferon pathway which is necessary for the clearance of viral infections, and may also speak to the importance of timing of the intervention. Results from the ongoing trial will provide further information regarding the use of these drugs for the treatment of COVID-19 (Table 6).

Granulocyte-monocyte colony-stimulating factor inhibitors

Granulocyte-monocyte colony stimulating factor (GM-CSF) inhibiting therapies are currently being studied for the treatment of rheumatic diseases such as RA and giant cell arteritis [57,58]. GM-CSF has been associated with severe COVID-19, and elevated levels have been associated with markers of endothelial injury and thrombosis [59]. Bronchoalveolar lavage fluid analysis from patients with severe COVID-19 has shown high levels of Th-17 cells associated with an overexpression of GM-CSF and IL-17A [60].

An initial study with lenzilumab (600 mg IV for three doses) in 12 patients with severe COVID-19 showed a faster improvement in clinical outcomes when compared to a matched control cohort receiving SOC (5 days vs 11 days, $P = 0.06$) [61]. Although clinical improvement was similar in both groups, the proportion of patients with ARDS was also reduced with lenzilumab treatment. The first published RCT assessing the use of a GM-CSF inhibitor, mavrilimumab, randomized patients to mavrilimumab vs SOC [62]. The Mavrilumab in patients with severe COVID-19 pneumonia and systemic hyperinflammation (MASH-COVID) study included hospitalized patients with COVID-19 pneumonia, hypoxemia, and CRP > 5 mg/dl. The primary outcome of survival without supplementary oxygen at day 14 was not different between the two groups (57% vs 47%, OR 1.48 [95% CI 0.43–5.16]. The results of this study were underpowered due to early termination after slow recruitment. Preprint results of two larger trials, LIVE-AIR (with lenzilumab) and OSCAR (otilimab), and ongoing studies will further clarify the role of GM-CSF inhibitors as treatment options for severe COVID-19 [63,64].

Anticomplement therapy

Complement activation has been shown to play a central role in the pathophysiology of both ARDS and macrovascular thrombosis. Endothelial injury secondary to activation of anaphylatoxins (C3a, C4a, and C5a) is a key component in the pathway of both of these complications [65▪]. Even more so, increased complement activation seems to be a distinctive feature of severe COVID-19 as shown by significant elevation of circulating markers of complement activation when compared to patients with other critical conditions, including influenza infection [66].

Use of eculizumab, a C5 inhibitor, for the treatment of severe COVID-19 has been described in several case reports. Eculizumab (900 mg, 2 doses) in addition to SOC was associated with recovery of four patients with severe COVID-19 [67]. In a nonrandomized controlled study of 80 patients with severe COVID-19, 35 patients treated with eculizumab vs 45 patients receiving SOC, patients treated with eculizumab had a higher survival at day 15 (82.9% vs 62.2%, $P = 0.04$) [68]. A phase 2 trial of IFX-1, a C5a inhibitor, showed no difference in its primary outcome of percentage change in PaFIO2, but showed a nonsignificant trend toward improved survival and decreased pulmonary embolisms [69]. Further knowledge of anticomplement therapies,

Table 6. Ongoing phase 3 or 4 randomized controlled trials assessing Janus Kinase inhibitor treatment in patients with COVID-19

Clinical Trials.gov Identifier/Study	Design	Intervention	Inclusion criteria	Primary outcome
Baricitinib				
NCT04421027	RCT/Hospitalized non-ICU	BARI 4 mg PO daily vs SOC	Confirmed SARS-CoV-2 infection, supplemental oxygen requirement, and at least one inflammatory marker > ULN: CRP, d-dimer, LDH, ferritin	Death or requirement of noninvasive ventilation/ HFNC or MV
NCT04358614	RCT/Hospitalized patients	BARI 4 mg PO daily for 14 d + antiviral vs antiviral	Confirmed SARS-CoV-2, radiographic infiltrates, SpO2 > 92%, PaFIO2 > 100–300 mmHg	Safety in terms of serious and nonserious adverse events
NCT04832880 AMMURAVID	RCT/ Hospitalized patients non-ICU	Dexamethasone (SOC) vs Remdesivir + SOC vs BARI 4 mg PO for 10 days + SOC vs Remdesivir + BARI + SOC	Confirmed SARS-CoV-2 infection, <10 days of symptom onset and Temple COVID-19 CS criteria	Composite outcome of Very severe respiratory failure (PaFIO2 < 150 mmHg) or mortality
NCT04693026	RCT/ ICU patients	Remdesivir + BARI 4 mg PO 14 days vs Remdesivir + TCZ	Confirmed SARS-CoV-2 + admission ICU	Time to clinical improvement
NCT04640168 ACTT-4	RCT/Hospitalized patients non-ICU	Remdesivir + BARI 4 mg PO 14 days vs Remdesivir + Dexamethasone	Confirmed SARS-CoV-2 + new oxygen requirement within past 7 days	Survival without MV and death
NCT04390464 TACTIC-R	RCT/Hospitalized patients non-ICU	BARI 4 mg PO 14 days vs Ravulizumab vs SOC	Suspected SARS-CoV-2 infection and severe disease	Time of incidence to composite endpoint of death, MV, ECMO, CV organ support or renal failure
NCT04890626	RCT/ Hospitalized patients	BARI + dexamethasone vs dexamethasone (SOC)	Confirmed SARS-CoV-2 infection	Death at day 28
NCT04891133 EU SolidAct	RCT/Hospitalized patients	BARI 4 mg PO 14 days + SOC	Confirmed SARS-CoV-2 infection + moderate-severe disease	Death at day 60
NCT04381936 RECOVERY	Open label-RCT/ Hospitalized patients	BARI 4 mg PO 10 days + SOC	Suspected or confirmed SARS-CoV-2 infection	All-cause mortality at day 28
Ruxolitinib				
NCT04424056 INFLAMMACOV	Open-label RCT/ Hospitalized patients	Ruxolitinib +/- TCZ or Anakinra vs SOC	Confirmed SARS-CoV-2 infection and hypoxemic pneumonia with CRP > 150 ng/ml or PAFIO2 < 300 or PaFIO2 < 200 with another organ failure	Ventilation free days at day 28

RCT, randomized controlled trial; BARI, baricitinib; SOC, standard of care; ICU, intensive care unit; SpO2, oxygen saturation; PaFIO2, ratio of arterial oxygen partial pressure to fractional inspired oxygen; TCZ, tocilizumab; CRP, C reactive protein; MV, mechanical ventilation; ECMO, extracorporeal membrane oxygenation; CV, cardiovascular.

including identification of biomarkers of patients who would benefit from these, are needed.

CONCLUSION

The unprecedented challenge of the global COVID-19 pandemic has rightfully monopolized the attention of the entire medical field. The hyperinflammatory features of severe COVID-19, somehow resembling those of rheumatic and cytokine storm syndromes, have placed both rheumatologists and the immunomodulatory medications used for the treatment of rheumatic diseases in a unique position. The successful use of glucocorticoids such as dexamethasone for the

treatment of COVID-19 has shown the benefits of immunomodulation. Interestingly observations such as those from the RECOVERY trial and large registries of patients with baseline glucocorticoid use (similar to JAK inhibitors), highlight the importance of timing of intervention. Even more so, studies have also shown the role of host characteristics, such as inborn errors in type I IFN immunity, therefore highlighting the need to better characterize patients at risk of COVID-19 hyperinflammation and potentially those who would benefit the most from immunomodulatory interventions [70▪,71▪▪].

Challenges to research during the COVID-19 pandemic have also left several valuable lessons that should be incorporated in future scenarios. As shown in this review, discordant results of trials assessing the same drug could be potentially explained by lack of uniform selection criteria, changes in definitions of SOC or changes in timing, dosages or duration of interventions. Understandably, the dynamic nature of the pandemic and knowledge generated has led to some of these limitations. However, coordinated efforts such as the RECOVERY adaptive trial platform have led to invaluable knowledge.

Although glucocorticoids have an established role in the treatment of severe COVID-19, other immunomodulatory therapies such as JAK inhibitors, particularly baricitinib, and IL-6 might require further studies despite some encouraging results. Particularly, studies are needed to better identify patients who would benefit from these interventions. Hopefully, ongoing RCTs or studies utilizing proposed COVID-19 hyperinflammatory phenotypic criteria will shed some light on this matter as well the role of other DMARDs such as IL-1, GM-CSF and complement inhibitors. Although approved vaccines are helping to mitigate the pandemic, the need to identify better treatment options for patients with severe COVID-19 and complications such as COVID-19 hyperinflammation remains crucial.

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Conflicts of interest

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The impact of the COVID-19 pandemic on the field of pediatric rheumatology

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Purpose of review
The purpose of this review is to discuss the clinical management of children with pediatric rheumatic disease (PRD) during the Coronavirus disease of 2019 (COVID-19) pandemic, as well as the unique role of the pediatric rheumatologist during a time of emerging post-COVID inflammatory sequelae including, multisystem inflammatory syndrome in children (MIS-C).

Recent findings
To date, there has been little evidence to suggest that children with PRD, including those on immunomodulatory therapies, are at increased risk for severe COVID-19. Clinical guidance statements have been created to support clinical providers in providing care to children with PRD during the COVID-19 pandemic. Pediatric rheumatologists have also been called upon to assist in the identification and management of post-COVID sequelae, including the rapidly emerging inflammatory illness, MIS-C.

Summary
The COVID-19 era has been defined by a rapid expansion in scientific knowledge and a time of extraordinary local and worldwide collaboration, both within the pediatric rheumatology community, as well as across multiple disciplines. Through collective efforts, we have learned that children with PRD, including those on immunomodulatory therapies, are not at increased risk for severe COVID-19. Pediatric rheumatologists have also worked alongside other disciplines to develop guidance for the management of MIS-C, with the majority of patients experiencing excellent clinical outcomes.

Keywords
COVID-19, multisystem inflammatory syndrome in children (MIS-C), pediatric rheumatic disease

INTRODUCTION

The global spread of Coronavirus disease of 2019 (COVID-19) abruptly impacted the pediatric rheumatology community, prompting physicians to rapidly assess the impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children with pediatric rheumatic disease (PRD) and the implications of immunosuppressive treatment on their risk for severe disease. Numerous questions arose surrounding preventive measures, risk reduction, ongoing immunosuppressive management, and methods to minimize disruption to clinical care. Simultaneously, pediatric rheumatologists quickly found themselves amidst the discovery of an unanticipated inflammatory syndrome related to COVID-19, now termed multisystem inflammatory syndrome in children (MIS-C). In a multidisciplinary collaborative effort with pediatric physicians including infectious disease and cardiology, pediatric rheumatologists have assisted in providing guidance surrounding the diagnostic evaluation and medical management of MIS-C. In this review, we will discuss the impact and clinical management of children with PRD during the COVID-19 pandemic, review the literature related to the clinical presentation and management of MIS-C, and briefly discuss unique clinical sequelae of COVID-19 that may prompt evaluation by a pediatric rheumatologist.

THE IMPACT OF COVID-19 IN CHILDREN WITH PEDIATRIC RHEUMATIC DISEASE

Since the onset of the COVID-19 pandemic, there have been concerns raised related to the potential

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KEY POINTS

- Children with PRD do not appear to be at significantly increased risk of severe COVID-19; thus, treatment goals should be targeted to assure optimal control of underlying PRD during the COVID-19 pandemic.
- The clinical management of MIS-C requires multidisciplinary collaboration with an appreciation of distinct clinical phenotypes to assure accurate diagnosis and immunomodulatory management.
- Post-COVID sequelae may manifest with inflammatory manifestations, mimicking pediatric rheumatologic disease, prompting assessment and recognition by pediatric rheumatologists.

impact of SARS-CoV-2 infection in patients with rheumatic disease and patients on immunosuppressive therapy. Reports in the literature of patients with adult-onset rheumatic disease have demonstrated that advancing age and underlying comorbidities remain a primary factor in the risk for severe complications from COVID-19, similar to the general population [1▪▪,2▪▪]. Few studies have also described disease-specific factors including underlying rheumatic disease, disease activity, the presence of lung involvement and certain immunomodulatory medications (including corticosteroids, rituximab and conventional disease modifying antirheumatic drugs (DMARDs)) that may additionally predict worse outcomes [2▪▪,3,4▪]. However, to date, there is little evidence to suggest a higher risk for severe COVID-19 in children with PRD [5–9] or children receiving immunomodulatory therapies commonly used for PRD [10–15].

In May 2020, the American College of Rheumatology (ACR) developed the ACR COVID-19 Clinical Guidance for Pediatric Rheumatology Task Force, charged to provide clinical guidance to rheumatology providers who treat children with PRD in the context of the COVID-19 pandemic [16▪]. Recognizing that children with PRD do not appear to be at significantly increased risk of severe COVID-19 and acknowledging the need to take into account individual patient characteristics and prevalence of SARS-CoV-2 transmission in the community, these general recommendations were aimed at assuring optimal control of underlying PRD during the era of the COVID-19 pandemic. Guidance was provided to discourage physicians from modifying or delaying immunomodulatory therapy in the absence of SARS-CoV-2 exposure or infection. Similarly, in the presence of close/household exposure or *asymptomatic* COVID-19, recommendations were to continue medical therapy needed to control underlying PRD, with special consideration to reduce corticosteroid burden to the lowest effective dose possible to control underlying disease. Concerns related to the use of rituximab and cyclophosphamide raised by the Global Rheumatology Alliance in adults with rheumatic disease [1▪▪] were acknowledged; however, given the overall reduced risk of severe COVID-19 in the pediatric population and the fact that these medications are typically reserved for severe life and/or organ threatening disease in children, the task force agreed that the benefits of continuing therapy likely outweigh the risk in most cases [16▪]. In contrast, in the presence of *symptomatic* COVID-19, the task force agreed to conform to conventional practices related to concurrent infections and recommended holding all DMARDs for the duration of symptoms and up to 7–14 days after resolution of fever and respiratory symptoms. Special considerations were made for patients with PRD on interleukin (IL)-1 inhibitors, as these patients may be particularly sensitive to medication disruptions and with the knowledge that selective IL-1 inhibitors have been safely used in other infections [17].

Another consideration that the pediatric rheumatologist faced in the era of the COVID-19 pandemic is the responsibility to assure adequate and timely access to clinical care, particularly during times of increased community transmission of SARS-CoV-2. In evaluating clinical practice and patient perspectives during the COVID-19 pandemic, both patients and families acknowledged that apprehension about in-person clinical assessments and safe access to the hospital system [18▪] may have resulted in delays to care and exacerbation of underlying illness [19]. As a result, the rapid expansion of telemedicine during this time has been instrumental in improving access to care for children with PRD [19–22], with the development of comprehensive telemedicine assessments, including standardizing the musculoskeletal physical exam using the video version of paediatric Gait Arms Legs and Spine (pGALS), V-pGALS [23▪]. Despite the numerous benefits of telemedicine, several limitations should also be acknowledged, specifically related to the quality and comprehensiveness of care, psychosocial evaluation, and the availability of access to technology to maintain health equity [21,24].

In addition to concerns related to medical management of children with PRD, the COVID-19 pandemic has also raised awareness of the impact emotional distress, school closures, and limited socialization on the overall well being of children with chronic illness. Children and adolescents with PRD have a relatively high prevalence of anxiety and depression at baseline compared to the general pediatric population [25,26]. Furthermore, there is evidence that patients within the

Black and Latinx populations may be disproportionately impacted by the pandemic from both a medical and psychosocial standpoint [18▪,27–30]. Pediatric rheumatology providers must be mindful of the burden of the COVID-19 pandemic on both children with PRD and their caregivers, recognizing the impact of psychosocial distress on physical disease, and assist with referrals to mental health services. Similarly, with regards to in-person schooling, the ACR COVID-19 Clinical Guidance for Pediatric Rheumatology Task Force recognized the generally low rates of transmission in primary and secondary schools [31] and emphasized the benefits of attending in-person school, once taking into account individual patient characteristics and comorbidities. Finally, to date, there has been no evidence to suggest children with PRD are at higher risk of adverse reactions from the COVID-19 vaccine and thus the task force recommended that children, adolescents, and young adults with PRD should receive the vaccine in accordance with Centers for Disease Control and local recommendations.

MULTI-INFLAMMATORY SYNDROME IN CHILDREN: THE ROLE OF THE PEDIATRIC RHEUMATOLOGIST

Since first described in Europe in April 2020, MIS-C (also known as pediatric multisystem inflammatory syndrome (PMIS)), has been increasingly recognized throughout the world. The presentation of MIS-C is temporally linked to COVID-19 exposure, with peaks of disease typically following surges of COVID-19 cases by approximately 3–6 weeks, and patients demonstrating evidence of prior SARS-CoV-2 infection with positive IgG serologies. Although MIS-C remains an overall rare condition, clinical presentations with cardiogenic shock and multiorgan dysfunction have created an impetus for rapid multidisciplinary collaboration and strategies to guide clinical management. Given the presentation of MIS-C as a systemic inflammatory condition with clinical symptomatology that often overlaps with Kawasaki disease, pediatric rheumatologists have been involved from the onset in attempts to understand the underlying pathophysiology, and have assisted in developing guidance for diagnostic evaluation, clinical monitoring and management with immunomodulatory therapy [32▪▪,33].

In the year since the initial description of MIS-C, knowledge regarding the presentation, management, and pathophysiology has rapidly expanded; however, numerous uncertainties remain. The majority of children presenting with MIS-C are previously healthy, with reports of prior asymptomatic or minimally symptomatic COVID-19; thus, underlying predisposing factors for MIS-C remain unknown. There is a range of clinical severity, yet a majority of patients require care in pediatric intensive care units (ICUs) during their hospitalization. Furthermore, while MIS-C was initially described as 'Kawasaki-like', numerous reports have studied these overlapping phenotypes and have since described differences in both clinical and immunochemical presentations between MIS-C and Kawasaki disease [34▪▪,35▪,36▪].

Current literature on MIS-C is represented by case reports, case series, and systematic reviews. In one of the largest systematic review to date, Hoste *et al.* summarized articles published on MIS-C/PMIS cases from December 2019 through August 2020 [34▪▪]. Median age at presentation was 8.4 years, with a large proportion of patients of Black (37%) and Latino/Hispanic (29%) descent. With the exception of obesity (25%), other comorbidities were rare. Nearly, all patients presented with fever (99%) and most commonly involved organ systems included gastrointestinal (86%), cardiovascular (79%), and respiratory (50%) (Fig. 1). In this systematic review, 23% of patients fulfilled criteria for complete Kawasaki disease, whereas 24.1% resembled incomplete Kawasaki disease. Laboratory evidence of systemic inflammation was evident in the majority of MIS-C cases, with elevated acute phase reactants including C-reactive protein, IL-6, and ferritin. Patients also had significantly elevated markers of coagulation (D-dimer, fibrinogen) and myocardial injury (troponin, brain natriuretic peptide).

Many investigators have compared children with MIS-C to historical Kawasaki disease patients. MIS-C patients tend to have a broader age range, with a median age range higher than that of classic Kawasaki disease (median age: 2–2.7 years) [34▪▪,35▪]. MIS-C patients are less likely to have coronary artery abnormalities and more likely to have ventricular dysfunction [35▪]. Evidence of systemic inflammation also appears to be substantially higher in MIS-C compared to historical Kawasaki disease cohorts. Studies have additionally compared clinical presentation, laboratory markers and outcomes in children and adolescents with MIS-C and acute COVID-19 [37,38]. Feldstein *et al.* compared cases of MIS-C in a USA cohort with severe acute COVID-19 and found that patients with MIS-C were more likely to be 6–12 years old, non-Hispanic/Black and more likely to be previously healthy [38]. Clinical symptoms that distinguished MIS-C patients from acute COVID-19 included mucocutaneous symptoms and severe cardiovascular involvement without respiratory involvement. Patients with MIS-C were more likely to have higher neutrophil-to-lymphocyte ratios, higher CRP levels, and lower platelet counts [38]. A summary of clinical and

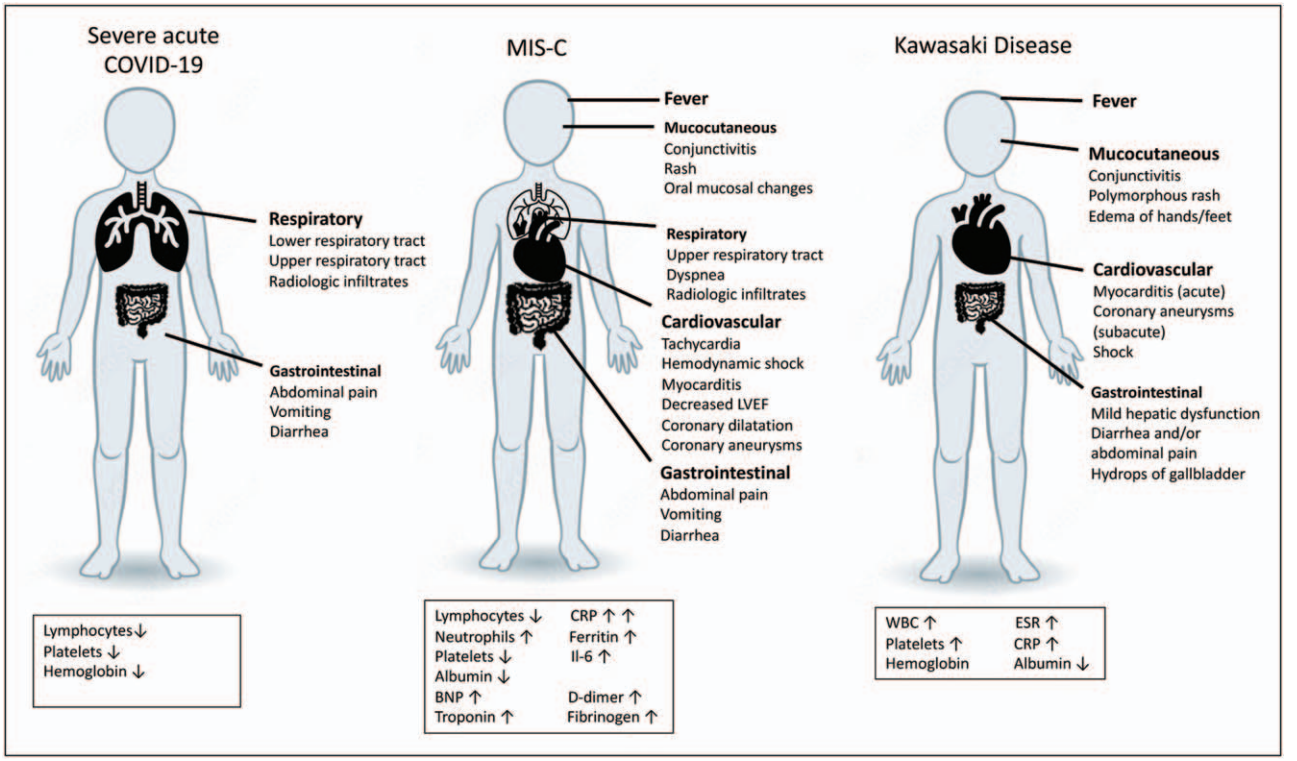

FIGURE 1. Summary figure of main clinical and laboratory findings in pediatric acute severe COVID-19 disease, MIS-C and Kawasaki disease. CRP, C reactive protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin-6; LVEF, left ventricular ejection fraction.

laboratory features of MIS-C, Kawasaki disease, and acute COVID-19 is presented in Fig. 1.

To date, immunomodulatory management of MIS-C has focused on its resemblance with Kawasaki disease and theoretical concerns about cardiac sequelae and potential coronary artery aneurysms, similar to those described with untreated KD. While data are limited to retrospective reports, case series, and anecdotal evidence, most reports describe widespread use of intravenous immunoglobulin (IVIG) and corticosteroids in 50–90% of patients for the treatment of MIS-C, with variability noted in treatment strategies and dosing among different centers and studies [33,34▪▪,35▪] One retrospective cohort study from France [39] compared use of IVIG alone versus IVIG plus methylprednisolone as initial therapy for MIS-C in propensity score-matched cohorts and found that combined therapy was associated with improved outcomes, including lower rate of treatment failure, lower use of second-line treatment, less need for hemodynamic support, less evidence of acute left ventricular dysfunction, and shorter ICU stay. IL-1 inhibition with anakinra has also been described in refractory disease in up to 8–26% of patients [34▪▪,35▪]. It is worth noting that a minority of patients in several case series have self-resolving inflammation and did not require immunomodulatory therapy. Other agents used less frequently include IL-6 inhibitors and tumor necrosis factor inhibitors [34▪▪]. Hoste *et al.* report the use of additional supportive care including inotropic agents (55%), mechanical ventilation (24%), noninvasive ventilation (26%), and extracorporeal membrane oxygenation support (4%) [34▪▪]. Although a majority of patients require ICU support (73%), almost all patients have excellent outcomes, with very few deaths reported and minimal long-term sequelae [40].

The ACR published clinical guidance for treatment of MIS-C and hyperinflammation in COVID-19 in June 2020 with revisions published in November 2020 [32▪▪]. This document includes a diagnostic pathway for MIS-C and a discussion of features distinguishing MIS-C from KD. Clinical guidance is provided for laboratory evaluation and cardiac monitoring, stratified by clinical presentation. Guidance for immunomodulatory therapy recommends stepwise approach with initiation of IVIG for all children hospitalized with MIS-C and/or fulfil Kawasaki disease criteria with careful consideration of cardiac function and fluid status to prevent fluid overload. Corticosteroids are recommended as first-line therapy for shock or organ threatening disease, or as a second line therapy for refractory disease

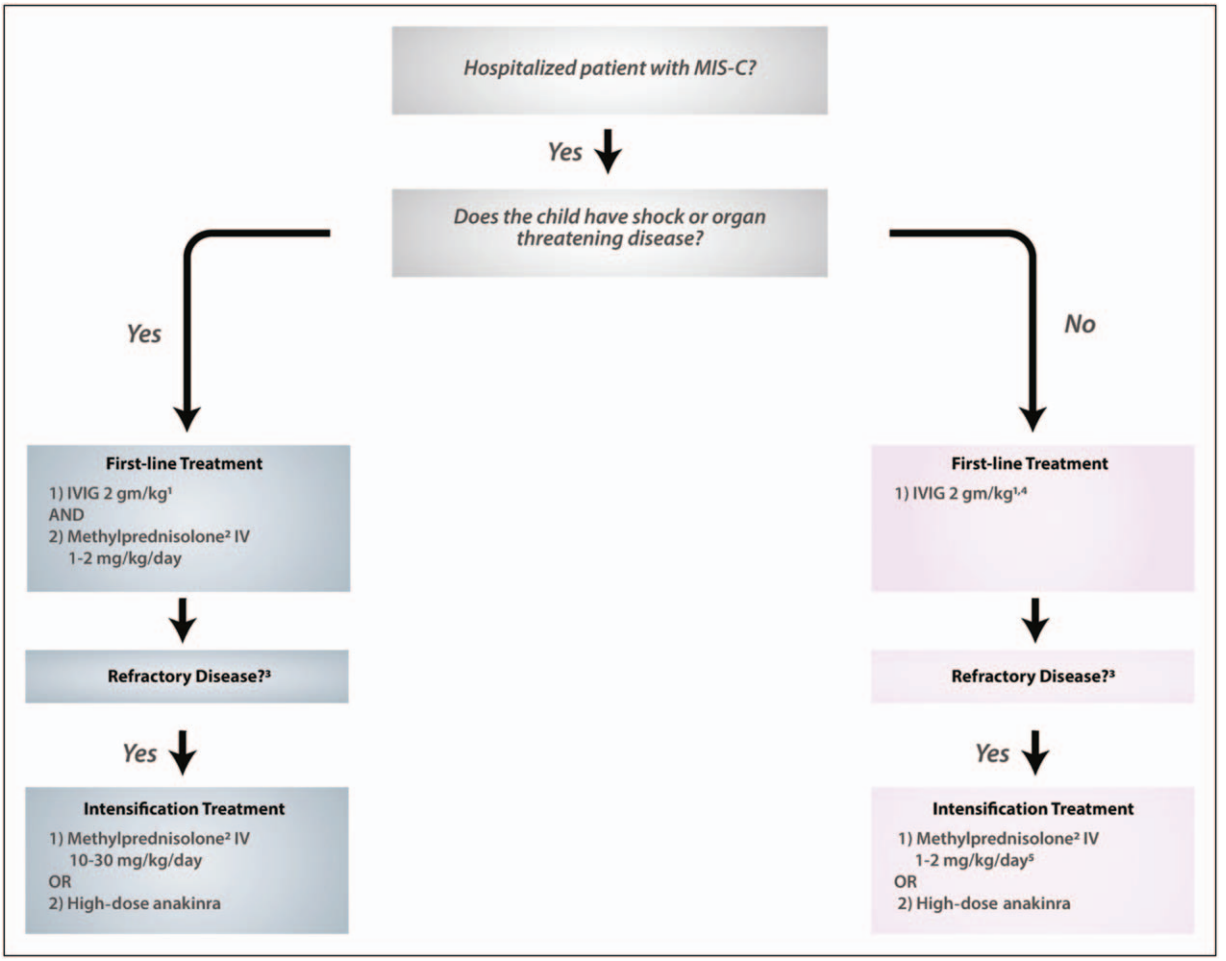

FIGURE 2. American College of Rheumatology (ACR) algorithm initial immunomodulatory treatment in MIS-C (original legend included in image). Algorithm for initial immunomodulatory treatment of multisystem inflammatory syndrome in children (MIS-C). Moderate-to-high consensus was reached by the Task Force in the development of this treatment algorithm for MIS-C associated with severe acute respiratory syndrome coronavirus 2. [1]Intravenous immunoglobuin (MG) dosing is 2 gm/kg based on ideal body weight. Cardiac function and fluid status should be assessed before MG is given. In some patients with cardiac dysfunction, MG may be given in divided doses (1 gm/kg da1y over 2 days). [2]Methylpremisolone or another steroid at equivalent dosing may be used. [3]Refractorry disease is defined as persistent fevers and/or ongoing and significant end-organ involvement. [4]Low-to-moderate-dose glucocorticoids (methylprednisolone 1-2 mg/kg/day) may be considered for first-line therapy in some MIS-C patients with concerning features (ill appearance, highly elevated B-type natriuretic peptide levels, unexplained tachycardia) who have not yet developed shock or organ-threatening disease. [5]If the patient was given low-to-moderate-dose glucocorticoids as first-line therapy, methylprednisolone IV dosing should be 10–30 mg/kg/day for intensification treatment. Reproduced with permission from Henderson *et al.* [32▪▪].

(Fig. 2). Other treatment options for refractory disease include high dose intravenous corticosteroids and IL-1 inhibition [32▪▪].

POST-COVID SEQUELAE

In addition to acute COVID-19 infection and post-infectious inflammatory conditions, post-COVID sequelae have also been described and are also being addressed by pediatric rheumatologists worldwide. Regardless of symptoms at diagnosis or severity of acute infection, several patients suffer from long-term effects of COVID-19. Rheumatologists are being called upon to assess a wide array of symptoms commonly seen as presentations of systemic autoimmune disease and to distinguish them from lingering effects of COVID-19. Symptoms vary among studies with fatigue, muscle weakness, sleep difficulties, and anxiety or depression commonly reported as long-term effects [41]. In a meta-analysis of studies world-wide, fatigue, headache, attention disorder, hair-loss, and dyspnea were the most common symptoms [42]. Although myalgia was the most common musculoskeletal symptom reported during acute COVID infection, many musculoskeletal findings have been reported as post-COVID

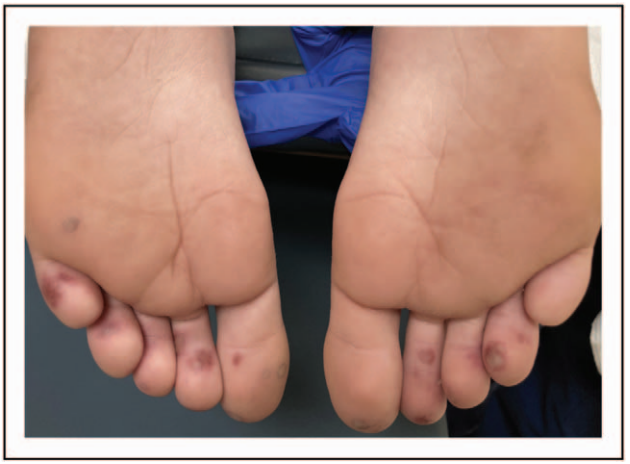

FIGURE 3. Clinical presentations of chilblains in an otherwise healthy young boy, presenting with pain and swelling in affected toes.

complications including myositis, neuropathy, arthropathy, and soft tissue abnormalities [43]. In children, data are scarce regarding long-term consequences of COVID-19 with few reports of fatigue, dyspnea, and heart palpitations or chest pain. Other symptoms reported include decreased concentration, prolonged fevers, and headaches [44].

Additional clinical features seen in both acute infection with COVID-19 and post-COVID sequelae are dermatologic manifestations that may mimic common rheumatologic conditions. The most common dermatologic findings in acute COVID-19 infection are maculopapular rash, urticaria, chilblains vesicular lesions, livedo reticularis, and petechiae. Interestingly, an increased incidence of chilblains has been reported during the pandemic and found to be more common in younger age patients [45]. Chilblains seem to appear after the active phase of disease, most commonly described in patients who were asymptomatic carriers of COVID-19 and found to have antibodies only after chilblains was reported. This entity has been termed 'COVID toes' and has been described in both adults and children (Fig. 3). Most pediatric cases present with no evidence of acute COVID-19 infection, and often with negative SARS-CoV-2 PCR testing and negative antibodies [46]. Histopathologic studies of these lesions have shown variable degrees of lymphocytic vasculitis with evidence of endothelial damage [47▪]. Coronavirus particles have also been described within the endothelium [47▪]. Prognosis of children with chilblains is favorable, with spontaneous regression within 2–8 weeks as the most common outcome. In severe cases, a trial of topical steroids and/or oral antihistamines may be considered [46,48].

CONCLUSION

Despite the numerous challenges to the medical community, the COVID-19 era has been defined by a rapid expansion in scientific knowledge and a time of extraordinary local and worldwide collaboration, both within the pediatric rheumatology community, as well as across multiple disciplines. Through collective efforts, we have learned that children with PRD, including those on immunomodulatory therapies, are not at increased risk for severe COVID-19; thus, the overall goals in the management of patients with PRD include continued therapy to assure prompt control of active disease, relief of symptoms, and prevention of long-term sequelae. Pediatric rheumatology providers must be mindful of challenges that have been exacerbated during the pandemic including healthcare inequities, impaired access to clinical care and psychosocial distress. Finally, pediatric rheumatology providers have been called upon to assist in the management of post-COVID sequelae, including MIS-C, relying on expertise in multidisciplinary collaboration, knowledge of immune responses, and the use of immunomodulatory therapies.

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Conflicts of interest

There are no conflicts of interest.

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