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Review

Safety and efficacy of pharmacological approaches available for multisystem inflammatory syndrome in children (MIS-C): a systematic review

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ABSTRACT

Background. To describe the existing pharmacological managements for Multisystem Inflammatory Syndrome in Children (MIS-C) in a systematic way, to identify the available pharmacological managements in MIS-C, evaluate its safety and efficacy and identify the best treatment procedures for practice recommendation.

Methods. A systematic search using six databases was conducted on August 18, 2021, updated in January 26th 2023. Terminologies that were used in this search are children, MIS-C/PIMS and SARS-CoV-2. A PRISMA flow diagram was used to report the study selection process. Quality analysis was done based on NOS and GRADE tools. Data synthesis was conducted by extracting the information on drugs used, efficacy and side effects.

Results. From the 32 articles included, a total of 2331 children with MIS-C were studied. The main pharmacological approaches were immunomodulatory therapy, i.e., intravenous immunoglobulin (IVIG) (77.3%), steroids (60.5%), and a combination of IVIG and steroids (41.3%). IVIG and steroids were found to be potentially effective and safe treatments for MIS-C. Combination of IVIG and steroids was found favorable in severe cases with higher recovery rate. Refractory treatments include second dose of initial treatment and biological response modifier drugs like anakinra, tocilizumab, infliximab. A small number of studies investigating supportive treatment consisted of vasoactive, inotropic and anticoagulation. The mortality rate was 1.28% and only three studies reported side effects from the treatment. Evidence of outcome from GRADE were mostly at moderate, low and very low levels.

Conclusions. This review provides preliminary evidence to support the current standard treatment practices in managing MIS-C pharmacologically. However, comprehensive investigation is required using clinical trials to provide stronger outcome evidence.

Key words: Multisystem Inflammatory Syndrome in Children (MIS-C), Paediatric Inflammatory, Multisystem Syndrome (PIMS), pharmacological treatment, systematic review.

Coronavirus Disease 2019 (COVID-19) became a global pandemic in early 2020.[1] Shortly, a newly recognized syndrome in children that causes severe multisystem inflammation and has clinical presentation like Kawasaki disease (KD) and toxic shock syndrome were reported.[2,3] This was then identified as a new disease associated with COVID-19 known as Multisystem Inflammatory Syndrome in Children (MIS-C). Alternately named pediatric inflammatory multisystem syndrome temporally associated with SARS- CoV-2 (PIMS-TS).

World Health Organization (WHO) criteria for MIS-C comprises, patients are less than 19 years old with fever (more than three days),

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inflammatory laboratory evidence, clinically severe inflammation that needs hospitalization, no other credible diagnoses and positive result for the SARS-CoV-2 infection.[4] The overlapping features between MIS-C and KD suggest that they may share a similar immunopathogenesis explaining their responsiveness to similar treatments.[3]

Unlike KD, cardiogenic or vasoplegic shock are prominent features in MIS-C, with majority of cases requiring hemodynamic support and intensive care admission. Nonetheless, survival rates are high and a mortality rate of 1-9% alone, has been reported.[5,6] However, there is concern on the harm and risk of MIS-C if treatment is not properly given. Moreover, there is a need to identify which treatment effectively reduces pharmaceutical waste resources and cost.

Currently, there are several suggestions on MIS-C treatments, pharmacological approaches, interventions and managements.[4,7,8] Yet no randomized trial is has been conducted to support the pharmacological approach for MIS-C. There are several reviews available pertaining to the topic.[1,9,10] However, they only provide an overall summary and narratively focus on the suggested treatment, as well as the epidemiological perspective. There is a limited understanding on the evidence level of available pharmacological treatment for MIS-C on its safety, efficacy and side effects.

This systematic review aims to describe the existing pharmacological managements for MIS-C in a systematic way, to identify the available pharmacological treatment approaches in MIS-C, evaluate its safety and efficacy and identify the best treatment procedure.

Methods

This systematic review was registered in International Platform of Registered Systematic Review and Meta-analysis (INPLASY202220052). The review question was developed using the patient/population, intervention, comparison and outcomes (PICO) model and determined as "What is the available pharmacological treatment for MIS-C and its level of evidence on the safety and efficacy?"

Searching and selection

Systematic search was done on six databases (Academic Search Complete, CINAHL, Cochrane Clinical Answers, Cochrane Database of Systematic Reviews, MEDLINE and Scopus). Manual searching was done by reviewing the reference list of included studies, other reviews and articles known by the authors. Search terms used were children MIS-C, PIMS and SARS-CoV-2. Inclusion criteria were studies reporting pharmacological treatment for MIS-C, being an original study, and involving patients age of 19 years and below. The exclusion criteria were non-English, no full-text available, grey literature (e.g., conference abstract, guideline), non-research article (e.g., editorial), and review articles. No restriction was imposed on study design. The search was initially done on August 18, 2021, and updated in January 26th 2023. Screening and selection were conducted independently involving at least 2 authors (YV, SA and GV) compared for pre-consensus agreement, disagreements were resolved by discussion. Other authors (MHR, PY and TK) validated the process through review. The process is reported using the PRISMA diagram.

Quality and Methodology Assessment

Methodological quality was assessed using the Newcastle-Ottawa Scale (NOS). NOS has eight items with multiple choices and scores. Each quality item choice in NOS is given a star with the top-quality research receiving up to nine scores. Among the eight items, any one of it can be given up to two stars. The score interpreted as good (7-9), fair (2-6) and poor (≤1). Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was also used in this review to analyse different clinical management treatments and to assess the certainty in evidence and strength of recommendations in health care.

Data extraction and analysis

Essential information from the included article has been extracted to a matrix table on study design, setting, main, refractory and supportive pharmacological treatment, outcome, side effects and assessed quality. Main treatments are defined as first treatments given and considered as the best treatment protocol. Refractory treatment used for refractory disease is considered when there is persistence fever or worsening of inflammatory markers and significant end organ involvement despite receiving initial treatment.[8] Supportive treatments are categorized as treatments used to control or prevent complications and side effects. Quality assessments were reported explicitly and overall limitations were identified. Narrative synthesis employed each pharmacological category on its evidence of efficacy and safety. Procedural aspects such as dosage, follow-up, side effects and precautionary measures were also synthesized.

Results

The systematic search resulted in a total of 2393 documents, and 32 studies being included with pre-consensus agreement of 88.3% (eDiagram in the supplementary information available online). Most studies have good and fair methodological quality (Mean: 6.5 Range: 5-8) according to NOS and the majority is at moderate, low, or very low evidence level according to GRADE (Table I). For methodological aspects most of the studies have issues on the accurate follow-up data. Most studies (71%) reported no follow-up data. Study design and lack of comprehensive reporting of treatment recommendations contributes to the poor GRADE level. Almost 75% of the studies were from developed and Western countries with a total of 2331 patients excluding a study[11] that surveyed the management protocols from 40 different centres in the United States. All studies included were conducted from March 2020 till January 2023. A detailed report on the included articles is presented in Table II.

Pharmacological Approaches

Table II shows the treatments used and the outcome for each of the included studies while the summarization of the treatments is reported in Table III.

• *Main treatment*

Intravenous immunoglobulin (IVIG) was the predominant treatment option used in 1839 of all patients (77.3%) in all studies in any combination as an anti-inflammatory measure with a dose of 2 g/kg or divided into two doses of 1g/kg. The overall evidence level supporting this was 4% good[12], 28% moderate[6,13-19], 36% low[11,20-29] and 32% very low.[30-41] IVIG alone was used in 902 patients (37.9%). Following that, 1439 patients (60.5%) received steroids in any combination as the main anti-inflammatory treatment. Out of these four hundred and four (16.9%) patients received steroids alone. A combination of IVIG and steroids were given to 43.1% of the total patients (72 % of the studies), which were preferred in severe cases. Methylprednisolone was the most common type of steroid used, which was administered with either low or high dose depending on the severity (1-4 mg/kg to 10-30 mg/kg). The evidence supporting the use of methylprednisolone was at good[12], moderate[6,14,17-19], low[22-24,27] and very low levels.[31,34,36] Another anti-inflammatory measure that was used in combination with IVIG was high dose aspirin (30-80 mg/kg/day) in 1.1% of the total patients.[15,19,24,35]

• *Refractory treatment*

A secondary infusion of the main treatment is given to patients who were unresponsive to the initial therapy. Patients were given a second dosage of IVIG as reported by 43% of the total studies.[6,11,12,15,17,21,27,32,34-37] Patients unresponsive to methylprednisolone were given a secondary infusion with similar or increased dosage in 29% of the studies.[12,17,18,22,27,32,34,35] Another immunomodulatory therapy that has been used for refractory disease is anakinra, an Interleukin-1 inhibitor which was given to

Table I. Quality analysis summary of the included studies using NOS and GRADE tools.

Article	Newcastle-Ottawa Scale (NOS)									GRADE		
	1	2	3	4	5	6	7	8	Total Score	Initial Quality	Upgrade/ Downgrade	Overall Quality
Ouldali et al. (2021)	a	a	a	a	a	a	b	d	6	C	↑↑	A
Cattalini et al. (2021)	a	a	a	a	a	a	a	b	8	C	↑	B
Emeksiz et al. (2021)	a	a	b	a	b	b	a	c	8	C	↑	B
Pouletty et al. (2020)	b	a	a	a	a	b	a	b	8	D	↑↑	B
Jonat et al. (2020)	a	a	a	a	a	a	b	b	7	C	↑	B
Ramcharan et al. (2020)	b	a	a	a	a	a	b	b	7	C	↑	B
Son et al. (2021)	a	a	a	a	a	a	b	d	6	C	↑	B
Vukomanovic et al. (2021)	b	a	a	a	a	a	b	c	6	C	↑	B
Lee et al. (2020)	a	a	c	b	a	a	a	d	5	C	↑	B
Balagurunathan et al. (2021)	a	a	a	a	a	b	a	b	8	C	-	C
Feldstein et al. (2020)	a	a	a	a	b	b	b	d	7	C	-	C
Savas Sen et al. (2021)	b	b	a	a	b	b	a	c	7	C	-	C
Borgi et al. (2021)	a	a	b	a	a	a	a	d	7	C	-	C
Kurz and Gombala (2021)	a	a	b	a	a	a	a	d	7	D	↑	C
Capone et al. (2020)	a	b	a	a	a	a	a	a	7	D	↑	C
McArdle et al. (2021)	b	a	b	a	b	a	b	c	7	C	-	C
Dove et al. (2020)	b	a	a	a	a	a	b	d	6	C	-	C
Angurana et al. (2021)	a	b	a	a	a	b	a	d	6	C	-	C
Kaushik et al. (2020)	a	a	a	a	a	c	b	d	5	C	-	C
Jain et al. (2020)	a	a	a	a	b	b	b	d	7	C	↓	D
Maskari et al. (2021)	a	a	b	a	a	b	a	d	7	D	-	D
Toubiana et al. (2020)	a	a	b	a	a	a	b	d	6	C	↓	D
Shobhavat et al. (2020)	a	a	b	a	a	b	b	d	6	D	-	D
Garcia-Dominguez et al. (2020)	a	b	b	a	a	a	a	d	6	D	-	D
Dhanalakshmi et al. (2020)	a	b	b	a	a	b	a	d	6	D	-	D
Cattaneo et al. (2021)	a	b	b	a	a	b	b	b	6	C	↓	D
Belhadjer et al. (2021)	a	b	b	a	a	a	b	d	5	D	-	D
Davies et al. (2021)	a	a	a	a	a	c	b	d	5	C	↓	D
Mehra et al. (2021)	a	a	a	a	a	a	b	a	8	C	-	C
Sethy et al. (2021)	a	a	a	a	b	a	b	d	5	C	-	C
Mane et al. (2022)	a	a	a	a	b	a	a	a	7	C	-	C
Ouldali et al. (2022)	a	a	a	a	b	a	b	a	7	D	-	D

(NOS: Selection- 1) Representativeness of the exposed cohort, 2) Selection of the non-exposed cohort, 3) Ascertainment of exposure, 4) Demonstration that outcome of interest was not present at start of study; Comparability- 5) Comparability of cohorts on the basis of the design or analysis and; Outcome- 6) Assessment of outcome, 7) Was follow-up long enough for outcomes to occur, 8) Adequacy of follow up of cohorts. GRADE (Grading of Recommendations Assessment, Development and Evaluation) quality: B- Moderate, C- Low, D- Very Low)

patients who were refractory to IVIG and steroids in 189 of the total patients (8.9%). A study reported the use of tocilizumab for patients unresponsive to anakinra.[14] Tocilizumab (IL-6 inhibitor), infliximab (TNF inhibitors) and rituximab were used in 92 patients (4.3%).

• ***Supportive treatment***

Vasoactive drugs (4.5%) such as epinephrine, norepinephrine and vasopressin were used as a supportive treatment modality in vasogenic shock cases while inotropic drugs (3.3%) such as milrinone and dobutamine were used in cardiogenic shock cases, reported in 16% of all the studies.[13,14,27,28,31,33,35] Anticoagulation (12.2%) was used in cases of severe left ventricular dysfunction, coronary artery aneurysm (CAA) or evidence of thrombosis complication with elevated d-dimer and fibrinogen levels. Besides, antiplatelet were administered to 5.3% of patients, while broad-spectrum antibiotics were taken by 6.8% of the patients. Antiviral and antimalarial treatments were used in 17 patients (0.6%) and 3 patients (0.1%), respectively.

Efficacy of treatment

The vast majority of children recovered under proper diagnosis and early treatment. The main outcomes focused on in this review are recovery reported on resolution in fever and other clinical manifestations, improved biochemical and cardiac parameters, as well as echocardiographic improvements of ventricular functions and resolution of coronary artery involvement. Other outcomes such median length of hospitalization/PICU stay were also reported in Table II. However, only 19 studies (59%) fully or partially reported data on recovery.[11,13-15,17-19,22-28,31,32,36-38]

Twenty-nine percent of the studies reported follow-up data either with good improvement in clinical findings and resolution of echocardiogram or partial resolution or with persistent heart abnormalities, although some of the follow-up data was incomplete. Fever, immunomodulatory markers, echocardiographic measures and other clinical signs were resolved on day 8 after treatment.[15] Vukomanovic et al.[18] reported that patients treated with corticosteroids had faster normalization of fever (afebrile on day 1) compared to patients treated with IVIG (afebrile on day 4) while Lee et al.[19] reported that patients treated with immunomodulators had fever that resolved after a median of 4 days. IVIG was found to be effective as first-line immunomodulator in treating MIS-C with inflammatory process improvements[19,33] followed by steroids (methylprednisolone) which is the most efficient in cases with shock or coronary artery aneurysm.[25]

However, a combination of these IVIG and steroids are best suggested to be efficient in severely ill cases.[6,12-16,19,20,22-24,26,27,30,32,35,37,38] This strategy is associated with quick fever resolution, low rate of treatment failure, reduced need for refractory treatment and rapid recovery of myocardial dysfunction compared to using IVIG or steroids alone.[27] Anakinra has therapeutic benefits with its efficacy in treating systemic inflammation and overall safety profile is evident.[6,12-15,19,21,22,25,28,30,37,38] Tocilizumab has shown encouraging benefits in patients with refractory disease.[15] Tocilizumab plays an important role as an IL-6 receptor inhibitor and efficiently mediates the cytokine storm and myocardial injury in patients with high IL-6 levels.[28] Infliximab was recommended as an alternative if IVIG was unavailable due to its efficacy in IVIG-resistant cases.[16]

There were not many studies focusing on the details or efficacy of supportive pharmacological treatment. Kaushik et al reported that the use of these vasopressors were associated with improvements by day 4 to 5 in most patients admitted.[28] Capone et al had found that low-molecular weight heparin (LMWH) is efficient in decreasing elevated levels of D-dimer or fibrinogen.[25]

Table II. General characteristics, primary and secondary treatment, outcome and side effects.

Author (year)	Population (Country)	Study type	Sample size	Treatment		Treatment	Outcome		
				Main	Refractory	Supportive	Recovery	Follow-up	Side effects
1. Ouldali et al. (2021)	Children (median age 8.6 years) (French)	Retrospective cohort	106	IVIG (2g/kg) IVIG + MP	IVIG second infusion IVIG + MP Anakinra Tocilizumab	Vasoactive or inotropic support (62% in IVIG+MP) and 32% in IVIG alone	IVIG + MP lower risk of treatment failure, OR [0.25(CI 0.09-0.7), P = 0.008) compared to IVIG alone Echo: Acute left ventricular dysfunction after initial therapy- 16/72(22.2%) with IVIG, 2/34(5.8%) with IVIG + MP. Median length of PICU stay- IVIG group is 6 days; IVIG + MP is 4 days. Mortality: None	No CVS complication in short term follow up	NR
2. Cattalini et al. (2021)	Children hospitalized with Kawasaki disease-like multi-inflammatory syndrome (Italy).	Observational Retrospective	53	IVIG GC IVIG + GC	Tocilizumab Anakinra	HCQ Antiviral Antibiotics Vasoactive Anticoagulation (Heparins) Low dose aspirin (ASA)	Good treatment response to GC and IVIG. Echo: Coronary involvement resolution. Mortality: None	Attended: NR 8 – persistent heart ultrasonography abnormalities	NR
3. Emeksiz et al. (2021)	Patients with severe MIS-C (Ankara, Turkey).	Observational, descriptive, retrospective	27	IVIG (1–2 g/kg) MP (30mg/kg/day) IVIG + MP	Anakinra Tocilizumab given to patients unresponsive to anakinra	Vasoactive drugs (epinephrine & norepinephrine) Anticoagulant (enoxaparin)	Improvement in clinical findings with immunomodulatory therapy. Median length of hospitalization is 15 days. Echo: 25/27 – complete recovery of ventricular function Mortality: 2	Attended: NR 8/27-clear stabilization of hemodynamics.	NR
4. Pouletty et al. (2020)	Children (median age 10 y/o) (Paris, France)	Multicen ter cohort, case series	16	IVIG Steroids IVIG + steroids High dose aspirin	IVIG second infusion Anakinra Tocilizumab	HCQ Low dose aspirin	All clinical signs resolved on day 8 after treatment. Mortality: None	Attended: 9/16 7 to 15 days: 9/9-asymptomatic. negative inflammatory biomarkers; 7/16 – normal heart ultrasounds; 2/16 – mild persistent cardiac dysfunction	Second infusion of IVIG-hemolytic anemia

Table II. Continued.

5. Jonat et al. (2020)	Pediatric patients (<21 y/o) (New York City)	Observational	54	IVIG GC IVIG + GC	Anakinra Infliximab	-	Clinical improvement of symptom resolution & improvement of shock with steroids. Median length of hospitalization is 4 days. Mortality: None	NR	NR
6. Ramcharan et al. (2020)	Children with PIMS-TS (United Kingdom)	Observational	15	IVIG (2 g/kg) MP	IVIG second infusion and/or three-day course of MP (In response to the first line IVIG)	Antibiotics Low dose aspirin	All have clinical improvement. Echo: 2/15- mild impairment LVEF at discharge; 3/15- abnormal ECG at discharge. Mortality: None	Attended: 12/15 12/15 - stable clinical and echocardiogram findings.	NR
7. Son et al. (2021)	Children (≤ 21 y/o) (United States)	Retrospe ctive cross- sectional	596	IVIG (2 g/kg) GC IVIG + GC	IVIG second infusion (2g/kg) Anakinra Infliximab Tocilizumab	-	Patients treated with IVIG + GC had a lower risk of receiving adjunctive treatment than IVIG alone. Echo: IVIG + GC was associated with a lower risk of cardiovascular dysfunction than IVIG alone. Mortality: 2	NR	NR
8. Vukoman ovic et al. (2021)	Children (average 13.2 ± 3.8 y/o) (Belgrade, Serbia).	Retrospe ctive cohort	22	IVIG GC (MP & dexamethasone)	GC: IVMP given to patients unresponsive to IVIG	-	Patients treated with GC had a faster normalization of fever than patients treated with IVIG (Day 1vs Day 4) Patients treated with CS had a rapid decline in proinflammatory parameters in the blood than patients treated with IVIG. 9/22 - Treatment failure (CS: 2, IVIG: 7). Mortality: None	NR	NR
9. Lee et al. (2020)	Children (1 month to 17 y/o) (Boston, United States).	Retrospective	28	IVIG (2 g/kg) MP (1–4 mg/kg/day) IVIG + MP High dose aspirin	Anakinra (5-13mg/kg/day)	Low-dose aspirin (3–6 mg/kg/day) enoxaparin Remdesivir HCQ	28/28- Clinical Improvement of inflammatory markers. Median length of hospitalization is 8 days. Echo: 3/6- Normalization of coronary vessel size after treatment (all 6 received IVIG, 4 received steroids) Mortality: None	NR	NR

Table II. Continued.

10. Balagurunathan et al. (2021)	Children (≤ 16 y/o) (South India).	Retrospective and prospective observational	21	IVIG Steroids IVIG + Steroids	-	Low dose aspirin Antibiotic Anticoagulant Antiepileptics	All with clinical improvement Median length of hospital stay: 6 days l Mortality: None	Attended: 16/21 16/16 - had 'no clinical concerns. 12/16 –echo partial or complete resolution from previous abnormalities.	NR
11. Feldstein et al. (2020)	Children (≤ 18 y/o) (United State)	Prospective, retrospective surveillance	186	IVIG GC	IVIG second infusion Tocilizumab Anakinra	Vasoactive support Anticoagulation	Majority recovered. 28% still hospitalized. Median length of Hospitalization: 7 days. Mortality: 4	NR	NR
12. Savas Sen et al. (2021)	Children (5.6 to 11.7 y/o) (Turkey).	Retrospective	45	IVIG (2 g/kg) IVIG + MP	MP given when Unresponsive to IVIG. Anakinra was used due to lack of adequate clinical response to previous IVIG and MP.	Anticoagulant (LMWH) Low dose aspirin (ASA)	I32/45 - recovered with IVIG alone. 45/45- had a favorable course. Mortality: None	NR	NR
13. Borgi et al. (2021)	Children (≤ 15 y/o) (South India).	Retrospective	8	IVIG (1 dose of 2 g/kg) + MP (10 mg/kg/day)	-	Low dose aspirin Dobutamine, Milrinone, Levosimendan Norepinephrine) Anticoagulant (LMWH) Antibiotic	All recovered with median length of PICU stay is 5.5 days. Echo: 8/8 - Complete recovery of left ventricular function was observed at a median delay of 4 days. Mortality: None	NR	NR
14. Kurz and Gombala (2021)	Children (2-18 y/o) (Vienna, Austria).	Case series	8	IVIG (2 g/kg) + high dose of MP (20–30 mg/kg) High dose aspirin (ASA, 30 mg/kg)	-	Antibiotics Anticoagulant (LMWH)	Rapid clinical improvement. Median length of hospitalization is 13 days. Echo: 8/8- function recovered Mortality: None	NR	NR

Table II. Continued.

15. Capone et al. (2020)	Children (United States)	Case series	33	IVIG CS	Anakinra Tocilizumab Infliximab	enoxaparin Aspirin	33/33- Rapid clinical improvement. Median length of hospitalization is 4 days. Echo: 14 had normal cardiac function, 10 had lower than normal cardiac function & 9 still have mild cardiac dysfunction at discharge. Mortality: None	Attended: 33/33 25/35 - complete recovery of left ventricle	NR
16. McArdle et al. (2021)	Patients with suspected MIS-C (a total of 32 countries).	Observat ional cohort	614	IVIG IVIG + GC GC	-	-	Decreased disease severity in patients treated with IVIG+GC (54/208) compared to patients treated with GC alone (20/99). Reduction of frequency of organ failure with GC benefits alone. Echo: NR Mortality: 12	NR	Drug complication occurred in 16/411patients who received GC in any combination and 9/508 patients who received IVIG in any combination- GC: Hyperglycemia-7 patients. Hypertension-7 patients. IVIG: Rash & lip swelling- 1 Anakinra: Superficial cutaneous infection- 1 Anticoagulation: Bleeding- 2
17. Dove et al. (2020)	Patients with MIS- C protocols (United States).	Cross-sectional survey	40 cent ers	IVIG (2 g/kg) CS	IVIG second infusion for cases that were refractory to the first dose. Tocilizumab Infliximab	Low dose aspirin Warfarin Remdesivir Antiplatelet Clopidogrel	Echo: Many patients have recovery of left ventricular systolic function at the time of discharge. Mortality: None	NR	NR

Table II. Continued.

18. Angurana et al. (2021)	Children (median age [IQR] age 7 months [5-10] (North India)	Retrospective	40	IVIG (2 g/kg) – 100% received IVIG. And combination with MP in 85% (10 -30 mg/kg/day)	IVIG second infusion given for non-improvement after first dose IVIG (2.5%) In patient received MP 10mg/kg/day, the MP dose was increased to 20 or 30 mg/kg/day. If there was no improvement in next 24-48 hours	Vasoactive 29/40 (72.5%) Low dose aspirin (3mg/kg/day) given in 80% Anticoagulant (LMWH) in 7.5% cases	Clinical improvements after treatment at discharge. Echo: Improvement in myocardial dysfunction but 6/40(15%) still have residual myocardial dysfunction at discharge Mortality: 2(6.2%)	NR	NR
19. Kaushik et al. (2020)	Children (median age 10 y/o) (New York City)	Retrospective, Cohort	33	IVIG IVIG + steroids Steroids	Anakinra Tocilizumab	Norepinephrine dopamine enoxaparin Antibiotics Remdesivir	Most patients showed improvements by day 4-5 with vasopressors. Median length of hospitalization is 7.8 days. Echo: Recovery of ventricular function & normalization of myocardial dysfunction. Mortality: 1	NR	NR
20. Jain et al. (2020)	Children with MIS- C with COVID-19 (Mumbai, India)	Cohort	23	IVIG Steroids IVIG + steroids	Anakinra Infliximab	Inotropic	Clinical improvements after treatment at discharge. Echo: 34.8% with LV dysfunction but no report on repeat echo Mortality: 1	NR	NR
21. Maskari et al. (2021)	Children (≤ 21 y/o) (Oman).	Case series	6	IVIG MP	Tocilizumab	-	Good clinical response within 24-48 hours. Range of hospital stay4-12 days Mortality: None	NR	NR
22. Toubiana et al. (2020)	Children (≤ 18 y/o) (Paris, France)	Prospective, observational	21	IVIG (2 g/kg) IVIG +steroids (2-10 mg/kg/day)	IVIG second infusion IVIG + steroids	Low dose aspirin (3-5 mg/kg/day) Vasoactive Inotropic Antibiotic	21/21- Rapid resolution of symptoms after treatment with IVIG. Median length of hospitalization is 8 days. Echo: NR Mortality: None	NR	NR
23. Shobhavat et al. (2020)	Children (West India).	Cohort	21	IVIG Steroids	Tocilizumab	Anticoagulant (LMWH) Aspirin	18/21 recovered with median length of PICU stay is 5 days. Echo: NR Mortality: 3	NR	NR

Table II. Continued.

24. Garcia-Dominguez et al. (2020)	Children with MIS- C associated a SARS- CoV-2 infection (Mexico).	Case series	4	IVIG (2 g/kg) MP (10 mg/kg)	Second infusion of IVIG and MP	epinephrine norepinephrine Antibiotics	4/4 – Responded adequately to IVIG, steroids, & vasopressors. 4/4 - Discharged without complications. Mortality: None	NR	2 patients developed acute kidney injury with recovery of kidney function 72 hours after IVIG & MP treatment.
25. Dhanalakshmi et al. (2020)	Children who met the case definition of PIMS- TS (Chennai, India).	Case series	19	IVIG (2 g/kg) Steroids IVIG + steroids	IVIG second infusion High dose steroids Tocilizumab	Antibiotics Aspirin	All recovered with median length of hospitalization is 6 days. Echo: NR Mortality: None	NR	NR
26. Cattaneo et al. (2021)	Children (≤ 18 y/o) (Mayotte Island, France).	Retrospective, descriptive	11	IVIG (2 g/kg) MP (2 mg/kg/day) Aspirin (ASA, 40–60 mg/kg/day)	IVIG second infusion (2 g/kg)	Inotropic Vasoactive Antibiotics Low-dose aspirin (5 mg/kg/day)	Median length of hospitalization is 8 days. Echo: 11/11 - Complete recovery of left ventricular function. Mortality: None	Attended: 8/11 8/8 – no cardiac abnormalities detected	NR
27. Belhadjer et al. (2021)	Children admitted to PICU (12 hospitals in France and 1 hospital in Switzerlan d).	Retrospective case series	35	IVIG IVIG + steroids	Repeated IVIG for persistent fever 48 hours after the first infusion; Anakinra	Inotropic Anticoagulant (Heparin)	28/35- Favorable clinical evolution. Median length of hospitalization is 10 days Echo: 7/35- Still in hospital/ with residual left ventricular dysfunction. Mortality: None	Attended: 28/35 25/35 -complete recovery of left ventricle (5/35: mild to moderate residual left ventricular systolic dysfunction)	NR
28. Davies et al. (2021)	Children (≤ 18 y/o) (United Kingdom)	Observational	78	IVIG Steroids IVIG + steroids	Anakinra Tocilizumab Infliximab Rituximab	Remdesivir	Median length of hospitalization is 5 days. Echo: NR Mortality: None	NR	NR
29. Sethy et al. (2021)	Children (Mean age of 9.09 years) (India)	Retrospective Observational	21	IVIG (2g/kg) MP (1-10 mg/kg/day) Steroids+ IVIG	NIL	Inotropic support (10/2147.6%) LMWH (10/21,47.6%)	17/2, 81% recovered Echo: 2 patients with myocardial dysfunction on discharge Mortality: 2	NR	NR
30. Mehra et al. (2021)	Children (< 18 y/o) (Delhi, India)	Retrospective, cohort Median age 7 (IQR: -10year)	120	IVIG Steroids No IVIG/ Steroids:	Non received tocilizumab or anakinra	Vasoactive Aspirin Enoxaparin/heparin, Remdesivir	96.6% survival outcome Mortality: 4	NR	NR

Table II. Continued.

31. Mane et al. (2022) (India)	Children with MIS-C	Case Series 2 month-9 year	7	IVIG MP		Inotropic Enoxaparin	5/7 patients improved with IVIG+/MP. 1/7 recovered without immunomodulator. Median hospital day: 7 days Mortality :1	NR
32. Ouldali et al. (2022) (French)	Children Age:12-17 years	Prospective national population-based surveillance following Covid-19 Vaccination	12	IVIG (2g/kg) + MP MP alone (3)	1 received MP(10mg/kg/day)	Antiplatelet dose (3-5 mg/kg) per	All recovered fully with median hospital length of stay 7 days IQR (7,9)	NR

ASA: acetylsalicylic acid, BNP: brain natriuretic peptide, CS: corticosteroids, ECG: electrocardiogram, Echo: echocardiography, GC: glucocorticoids, HCQ: hydroxychloroquine HSP: Henoch- Schoenlein purpura, IM: inflammatory markers, IVIG: intravenous immunoglobulin, IVMP: intravenous methylprednisolone, KD: Kawasaki disease, LMWH: low molecular weight heparin, LVEF: left ventricular ejection fraction, MIS-C: multisystem inflammatory syndrome in children, MP: methylprednisolone, NR: not reported, PICU: Paediatric Intensive Care Unit, PIMS-TS: paediatric inflammatory multisystem syndrome, WHO: World Health Organization.

Safety and Side Effects

Several precautions need to be taken to ensure the treatments are safe to be utilised. Consultation with specialists is crucial in cases of giving drug combinations with higher dosage as it is less safe. Ramcharan et al.[17] described the use of milrinone in patients with vasogenic shock as the drug is known to produce a counterproductive effect of peripheral vasodilation.

Only three studies reported side effects from the pharmacological treatments given (Table II). Hemolytic anemia was observed in one patient who received a repeated dose of IVIG.[15] Drug complications occurred in 16 patients who received glucocorticoids and 9 patients who received IVIG in any combination.[26] One patient developed acute kidney injury following IVIG and methylprednisolone treatment.[34]

The reported mortality was 30 out of 2331 patients (1.28%). Due to the severity of SARS-CoV-2-associated MIS-C, it is critical to diagnose and treat it as soon as possible.[14] Angurana et al.[27] reported death in their cohort by highlighting the importance of early recognition and timely diagnosis. Another study reported the death of MIS-C patients with shock and possibly due to late admission to hospital.[33]

Discussion

MIS-C is rare with serious inflammatory complications that manifests late following SARS-CoV-2 infection (SARS-CoV-2). This has been postulated as post-infectious immune dysregulation characterized by a hyperinflammatory cytokine storm and macrophage activation in genetically predisposed children. Since the novel coronavirus was identified in late 2019, various COVID-19 variants had been reported, i.e., Ancestral type, Beta, Delta, and the latest Omicron. However, a study comparing the clinical phenotype of MIS-C in children across four distinct variant-driven waves reported that regardless of variant, MIS-C remains a severe disease with a stable clinical presentation.[42]

Auspiciously, compared to Alpha wave, MIS-C was less common in the waves driven by Delta and Omicron.[43] In addition, Zambrano et al. reported that the introduction of Covid-19 mRNA vaccine in children and adolescents is protective against MIS-C.[44]

The pharmacological approaches of MIS-C were extrapolated from KD treatment as they may share some immunopathogenesis, however, both demonstrated distinct epidemiology, clinical manifestations, and laboratory markers. Compared to KD, cardiogenic or vasoplegic shock are prominent features in MIS-C, with 60-75% of cases requiring hemodynamic support that may be responsible for the mortality.[45] Main treatments consist of immunomodulatory therapy aimed at decreasing tissue inflammation that aid in tissue recovery and supportive management of acute life-threatening complications and prevent long-term sequelae like CAA.[9] The pharmacological approach of MIS-C has been strongly influenced by recommended KD management in which IVIG and aspirin are the standard first-line treatments; whereas corticosteroids and/or biological response modifier drugs (BRMDs) are indicated in a case of IVIG refractory or high-risk cardiac complication. However, MIS-C has a refractory nature due to a greater degree of inflammations with more severe multiorgan involvement such that most children require corticosteroids as part of main treatments.[46] On the other hand, a few studies reported that treatment with steroids alone is a plausible initial treatment for MIS-C.[26,38] A progressive approach for MIS-C management with immunomodulatory therapy is indicated based on the severity of clinical manifestation or MIS-C spectrum. The findings from this review are in line with published guidelines.[8,47] We have demonstrated that immunomodulatory therapy effectively treats MIS-C with a low risk of side effects. However, the available data was limited to nonrandomized studies with evidence using GRADE that was mostly at low and moderate levels.

Main Immunomodulatory Therapy

• *Intravenous Immunoglobulin (IVIG)*

IVIG is a blood product composed of purified serum immunoglobulin G protein, which serves as an immunomodulator of both innate and adaptive immunity.[48] IVIG can be substituted from pro-inflammatory to anti-inflammatory due to its cytotoxic properties towards neutrophils and eosinophils.[49] In cellular immunity, IVIG inhibits the activation of monocytes and macrophages. It also triggers the release of anti-inflammatory cytokines from innate cells that give rise to a reduction in macrophage response towards interferon.[49]

IVIG is suggested to be used as the first-line of pharmacological treatment for MIS-C.[33] We demonstrated that 38.2% of the study population received IVIG alone. However, in several studies, MIS-C patients did not respond to IVIG treatment.[12,18,50] Early addition of glucocorticoids to IVIG therapy resulted in fever resolution and significant decrease in inflammatory markers[18], whereas other studies found that a combination of IVIG and glucocorticoids caused lower risk of fever recurrence, cardiovascular dysfunction, and the need for adjunct treatment.[6,12] In addition, other studies reported that early administration of IVIG and glucocorticoid in MIS-C is related with a decrease in ICU admissions and length of hospital stay.[12,16] Simon et al. suggested that MIS-C patients who are at high risk of developing immunoglobulin resistance should be given a combination of IVIG and steroids, which appears to lower the incidence of coronary anomalies and the duration of fever.[51]

Therefore, early intensified therapy with combination of IVIG and steroids are beneficial in more severely ill patients and who are at high risk of developing immunoglobulin resistance. A recent study on the trends of MIS-C treatment for patients who required ICU admission in the United States, demonstrated increased practice of using combination of IVIG and steroids from 43% in April 2020 to 76.1% in Jun 2021 and the

proportion of patients who received IVIG alone decreasing from 22% to only 6.5%.[52]

In refractory cases associated with unresolved fever or symptoms, a treatment protocol of secondary infusion of IVIG within 2 to 3 days has been suggested.[9] In this review, 43% of the total studies used a second infusion of IVIG in refractory cases.[6,11,12,15,17,21,27,32,34-37] The need for higher doses of IVIG is related to body size and age of the patients which may increase the risk of volume overload, particularly for cases with underlying myocardial dysfunction.[47] Therefore, it is suggested that fluid status and ventricular function should be assessed prior to IVIG administration to avoid complications of fluid overload.

Furthermore, high doses of IVIG can also be associated with hemolytic anemia, however, only one patient in a study by Pouletty et al.[15] reported this side effect in our review. According to the clinical guidance of American College of Rheumatology (ACR)[8], MIS-C patients with refractory disease are not recommended a second administration of IVIG. Alternatively, glucocorticoids with low-moderate doses may be considered. Despite that, a recent study on treatment trends of MIS-C in the United States showed that IVIG is the most utilized treatments, administered to 85.6% of patients and about 18.1% received a second dose of IVIG.[52]

- ***Glucocorticoids***

Glucocorticoids usage has a tendency to decrease the development rate of CAA in patients with classical KD with increased risk of resistance to IVIG.[47] Molecules associated with inflammation such as cytokines, metabolites and chemokines are hindered by glucocorticoids.[53] Mechanisms of glucocorticoids are mainly moderated via classic glucocorticoid receptors. Glucocorticoids have anti-inflammatory effects that are said to result from transrepression- a vital negative regulatory mechanism.[54] The rapid action of glucocorticoids enables the reduction in hyperinflammatory response, inhibits vasodilation and increases permeability via inhibition of IL-1α and IL-1β.[55]

Vukomanovic et al.[18] investagated the infusion of corticosteroids as a first-line treatment for MIS-C patients with cardiovascular involvement. In comparison to IVIG-treated patients, glucocorticoids were linked with faster normalisation of fever, laboratory parameters, cardiac function and shorter ICU stays. Based on a study, there was also no evidence of delayed recovery from organ failure in individuals who received glucocorticoids alone as their first therapy.[26] In this systematic review, almost 17.3% of patients received steroids alone.[6,11,13-21,25,26,28,30,31,33-36,38] Some children with shock who required numerous inotropes and/or vasopressors reacted best to large doses of intravenous glucocorticoids (10–30 mg/kg/day).

Intravenous glucocorticoids with high doses have been used safely and successfully in MIS-C, KD and shock patients.[16,56,57] Given these findings, treatment with just steroids is plausible to be considered as an initial treatment for MIS-C. Nevertheless, rather than following predefined protocols, having a personalized treatment for each patient is equally crucial, coordinated by a multidisciplinary team.[9]

According to ACR guidance[8], low to moderated dose of glucocorticoids (1-2 mg/kg/day) should be added early to IVIG treatment in MIS-C cases that require hospitalization and high dose glucocorticoids (10-30 mg/kg/day) in refractory cases. High dose may be considered as an emergency and immediate treatment for budget-constrained regions as their access to IVIG is limited. Many lower and middle-income countries have issues with adequate and proper medication supplies, therefore, there is a need for randomized control trials to study if steroids or IVIG alone or combination groups are more effective than others.[26,38] More evidence to assist the use of cheaper anti-inflammatory groups such as glucocorticoids is needed. In this systematic review, commonly reported side

effects from corticosteroids were hypertension and hyperglycemia in a very small number of patients. Only one patient developed acute kidney injury from using the combination of IVIG and steroids.[34]

• ***Aspirin***

Salicylate is the active ingredient of aspirin which is responsible for the anti-inflammatory activity.[58] It is a member of a large family of pleiotropic and short-lived mediators that are produced by the cell membrane's arachidonic acid moiety and have biological effects on a variety of cell types, including platelets and endothelial cells. By suppressing cyclooxygenase enzymes, lipid mediators are synthesized such as thromboxane, prostacyclin, and prostaglandin; which also possesses anti-inflammatory, antipyretic, and antiplatelet activities.[59] High dose aspirin has been used as a treatment option for anti-inflammatory effects in KD and Rheumatic carditis. However, an anti-inflammatory dose of aspirin is not part of ACR recommendations in MIS-C management. It has been received by only 1.1% of the total patients in our review, mostly in the initial phase of MIS-C where treatment depends strongly on the KD treatment protocol.

• ***Biological Response Modifier Drugs (BRMDs)***

BRMDs are a novel class of therapeutic treatments that include recombinant human monoclonal antibodies or receptor antagonists and have been utilized to treat a number of autoimmune disorders.[60] MIS-C can lead to immune-mediated multiorgan damage[61], hence, immunomodulatory therapy is recommended such as anakinra, tocilizumab and infliximab as recommended by the ACR in refractory treatments.[8,47] Patients with severe inflammation and refractory disease are recommended to consult rheumatologist and/or immunologist when considering immunomodulatory beyond required dosage with anakinra.[16] However, there is very limited evidence to suggest that anakinra is more preferable compared to other biological immunomodulatory agents such as infliximab in effectively treating MIS-C.[16,62] Anakinra is more preferable than glucocorticoids in patients with sickle cell anemia because glucocorticoids are reported to have a tendency of complicating vaso-occlusive pain crises.[19] Compared to ACR, the United Kingdom's PIMS-TS National Consensus Management Study Group recommend the use of a second dose of IVIG with preference of infliximab over anakinra for refractory cases of KD-like phenotype presentation.[63] Currently, there is ongoing clinical trials to investigate the effectiveness of infliximab, methylprednisolone, anakinra, and tocilizumab in MIS-C patients.[64]

Supportive Therapy

Therapeutic anticoagulants that were used in the studies were LMWH, enoxaparin and warfarin (12.1% of the patients). It should be heavily considered for patients with evidence of thrombosis ,giant CAA or ventricular dysfunction.[45] As recommended by the ACR, anticoagulants should be given to high-risk patients, however, patients' risk for bleeding should be taken into consideration.[8] A study by Abrams et al. on trends of MIS-C treatment in US, about 88% of 2000 patients were treated with anticoagulant, the majority received enoxaparin (86.8%) followed by heparin (18.9%), rivaroxaban(3.2%) and apixaban(1%).[52]

Low-dose aspirin is recommended for MIS-C to reduce the risk of thrombosis.[65] Patients who fit the criteria for KD, have coronary artery abnormalities, or who have additional thrombosis risk factors may be considered for antiplatelet treatment.[45] According to ACR, aspirin with a low dose of 3-5 mg/kg/day not exceeding 81 mg/day is recommended to be utilised in MIS-C patients and continued up till platelet counts and coronary artery return to normal.[8] However, only 5.4% of the patients in this review received this treatment. The low result could be explained by lack of reporting or detailed information. The current trend of MIS-C treatment in the US, demonstrated that 73.7% of 4901 patients with suspected MIS-C received an antiplatelet dose of aspirin.[52]

Table III. Summary of pharmacological treatments identified and its usage.

Treatment	Usage, n/2331 (%)	Studies used, n/32 (%)
Total IVIG [6,11-37]	1958 (84%)	32 (100%)
IVIG alone [6,11-22,25-37]	902 (38.7%)	267 (84%)
Total Steroids [6,11-37]	1439 (61.7%)	32 (100%)
Steroids alone [6,11,13-21,25,26,28-30,32-35,37]	404 (17.3%)	27 (84%)
IVIG + Steroids [6,12-16,19,20,22-24,26,27,29,31,34,36,37]	982 (42.1%)	23 (72%)
High dose Aspirin (Anti-inflammatory) [15,19,24,35]	26 (1.1%)	4 (13%)
Anakinra [6,12-15,19,21,22,25, 28,29,36,37]	189 (8.1%)	13 (41%)
Tocilizumab, Infliximab, Rituximab [6,11,12,14,15,21,25,28-30,32,34,37]	92 (3.9%)	13 (41%)
Anticoagulation (LMWH, enoxaparin, warfarin, heparin, etc.) [11,13,14,19-25,27,28,32,36]	257 (11%)	14 (44%)
Low dose Aspirin (Antiplatelet) [11,15,17,19,22,23,27,31,35]	126 (5.4%)	9 (28%)
Unspecified Aspirin [13,20,25,32,34]	86 (3.7%)	5 (16%)
Vasoactive drugs (epinephrine, norepinephrine, vasopressin, etc.) [13,14,27,28,31,33,35]	105 (4.5%)	7 (22%)
Inotropic drugs (milrinone, dobutamine) [23,29,31,35,36]	78 (3.3%)	5 (16%)
Antibiotics [13,17,20,23,24,28,31,33-35]	162 (6.9%)	10 (31%)
Antiviral drugs (remdesivir) [11,13,19,28,37]	17 (0.7%)	5 (16%)
Antimalarial drugs (hydroxychloroquine) [13,15,19]	3 (0.1)	3 (6%)

Inotropic agents such as dobutamine and milrinone are efficient in improving echocardiographic measures of patients with severe left ventricular dysfunction. A patient with severe cardiac dysfunction can require more than one inotropic drug.[23] Milrinone is an inotropic agent and a vasoactive drug which aids in increasing cardiac output by vasodilation and its inotropic effect. However, milrinone is known to produce a counterproductive effect of peripheral vasodilation as a side effect.[17]

Antibiotics are found to be efficient in cases of bacterial infections. In cases of patients with shock, antibiotic administration plays an important role and cannot be delayed.[51] The role of antiviral efficacy such as remdesivir is currently not evident.[61] These treatments do not contain any evidence that can be used to treat MIS-C.[11,13,19,20,38]

This current review can serve as preliminary evidence in supporting the major pharmacological treatment for MIS-C. However, the findings should be accepted cautiously as evidence available is limited due to methodological design. The reliance on observational studies and pharmacological approach is most likely limited to moderate and severe cases with limited long term follow up. The absence of high-quality studies such as large-scale prospective longitudinal studies or randomized controlled trials, warrant for more studies to be conducted to provide more confidence on the medication efficacy and safety. Another limitation of this current review is on the inability to conduct meta-analysis due to insufficient data availability and designs of the included studies. However, this review is still valuable in giving pharmacological treatment suggestions for MIS-C, especially with the discussion on its safety, potential side effects, and current guidelines or trends in pharmacological management.

In conclusion, IVIG or steroids alone, or combination of the two were found to be effective and relatively safe as the main MIS-C treatment. In severe refractory conditions, second infusion of the main treatment and biological response

modifier drugs should be considered in a stepwise approach. However, majority of included studies were at moderate, low, or very low evidence levels according to GRADE. Therefore, comprehensive investigation using randomized clinical trials are required to provide stronger outcome evidence.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: PY, YV and MHR; data collection: YV, GV, PY and SA; analysis and interpretation of results: MHR, PY, YV and KT. Author; draft manuscript preparation: YV, GV, PY, MHR and KT. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

Supplementary information

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