Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
Funded by the Department of Health

EVIDENCE SUMMARY

RESEARCH QUESTION: **Among multisystem inflammatory syndrome in children (MIS-C) patients, should intravenous immunoglobulin (IVIg) and steroids be used?**

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RECOMMENDATIONS

Recommendations	Certainty of Evidence	Strength of Recommendation
We suggest the use of steroids (methylprednisolone) among children diagnosed with multisystem inflammatory syndrome in children.	Very Low	Weak
We suggest to offer the use of IVIg in combination with steroids among children diagnosed with multisystem inflammatory syndrome associated with significant organ involvement*. *Based on six cohort studies, patients with MIS-C who received combination of steroids and IVIg had more severe initial presentation, with more frequent initial acute left ventricular dysfunction, ICU care upon admission, and requirement of hemodynamic support upon admission [16]; higher troponin levels, and higher need for inotropes upon admission [10]; high proportion of patients with abnormal inflammatory mediators on admission [14]; lower mean ejection fraction at baseline, lower platelet counts, and higher CRP and ferritin [15]; significantly more extensive organ involvement (higher frequency of respiratory, ocular and cardiovascular involvement) [20]; and higher cases of severe MIS-C, lower platelet and lymphocyte count, and higher CRP [19]	Very Low	Weak

Consensus Panel Issues

It is recognized that MISC and Kawasaki Disease in children have similarities hence the use of steroids and IVIg was postulated to improve outcomes for MISC. However, the available evidence shows benefit only for steroids with inconclusive results for the use of IVIg. Combination therapy may be offered in MISC with significant organ involvement but **it is important to note that this is based only on six cohort studies (very low certainty of evidence) and only with a trend towards benefit on non-critical outcomes**. The presence of concomitant Kawasaki Disease should be ascertained and identified as this would entail the use of IVIg which is considered standard of care.

KEY FINDINGS

- One randomized controlled trial (RCT) compared the use of steroid versus IVIg in the treatment of MIS-C. A significant decrease in need for respiratory support, a critical outcome, was noted in patients given steroids alone. Moreover, there is no significant difference between steroids and IVIg in terms of presence of serious adverse events, length of hospital stay, need for intensive care unit (ICU) admission, and duration of respiratory support. Quality of evidence was very low due to presence of serious risk of bias due to lack of blinding in the patients, caregivers, and outcome assessors, low sample size, and use of a single small study.

- Seven retrospective cohort studies explored the effect of IVIg plus steroid versus IVIG alone in the treatment of children diagnosed with MIS-C. IVIg plus steroids showed significantly less persistent

fever and reduced need for adjunctive therapy, which were both important outcomes. Meanwhile, the combined therapy did not show significant difference in reducing mortality, need for mechanical ventilation, hospital length of stay, need for ICU admission, and the need for vasopressor versus IVIg alone. Evidence has serious risk of bias, due to the study design, imprecision, and inconsistency of the outcomes hence the quality is very low.

- Four retrospective cohort studies compared the use of steroid alone versus the combined IVIg plus steroid in the treatment of MIS-C. There was no noted significant difference between the two groups in any the critical and important outcomes: mortality, need for mechanical ventilation, hospital length of stay, need for ICU admission, need for vasopressors, persistence of fever and need for adjunctive therapy. However, there was a trend towards benefit with the combined IVIg plus steroid in the need for ICU admission and trend towards benefit with steroids alone in terms of persistence of fever. Quality of evidence was very low due to the serious risk of bias due to the study design, imprecision, and inconsistency of the outcomes.

- Pertinent in the population used for the combined IVIg plus steroid group in six cohort studies (Parts 2 and 3), was the significant organ involvement and a more severe disease presentation upon admission.

INTRODUCTION

Multisystem inflammatory syndrome in children (MIS-C) is a rare but serious complication of severe acute respiratory coronavirus 2 (SARS-CoV-2) first described in April 2020 [1-5]. It is also referred to as pediatric inflammatory multisystem syndrome temporally related with SARS-CoV-2 (PIMS-TS). The pathophysiology is still unclear but is attributed to abnormal immune response to the virus [6]. There are various published case definitions for MIS-C as described by the World Health Organization (WHO), Center for Disease Control and Prevention (CDC) and the Royal College of Pediatrics and Child Health (RCPCH) [1-4]. Pertinent manifestations in all case definitions are the following: persistent fever, elevated inflammatory markers, multisystem organ involvement, presence of current or past SARS-CoV-2 infection, and exclusion of other plausible diagnosis [1-4]. Gastrointestinal, mucocutaneous, neurologic, cardiovascular, pulmonary, and hematologic symptoms were reported, some with multiorgan failure and shock requiring hospitalization and intensive care [1,6-7]. Clinical presentation of MIS-C was noted to mimic Kawasaki disease hence IVIg was suggested as one of its treatment choices [1,5-6,8-9]. Aside from IVIG, other immunomodulators, anti-inflammatory agents, and their combinations have been suggested as treatment for MIS-C [8,10]. Currently, there is insufficient evidence to support the use of any of the suggested treatment strategies.

REVIEW METHODS

A comprehensive and systematic search was done from January 20 – May 4, 2023, via Medline, Cochrane Library, COVID-NMA and Google Scholar using the following key terms: pediatric multisystem inflammatory disease, COVID-19 related [MeSH], MIS-C, immunoglobulins [MeSH], and steroids [MeSH]. Ongoing studies and preprints were also investigated using the following sites: clinicaltrials.gov, clinical trial registries, Chinaxiv, Medrxiv, and Biorxiv. Secondary search was done by screening the references of the initially retrieved articles (see Appendix 2 and 3).

RCT and cohort studies comparing steroid vs IVIg, IVIg plus steroid vs IVIg alone, and steroid vs IVIg plus steroid were included. Population investigated were children who met any published criteria for MIS-C with critical outcomes such as mortality, need for mechanical ventilation and serious adverse events. In addition, the important outcomes reviewed are as follows: clinical improvement, clinical deterioration, and duration of mechanical ventilation. No limit on the type and dose of steroid used were placed. Appraisal of the randomized controlled trials were done using the risk of bias tool from Revman 5 software [11], while the Newcastle-Ottawa Scale (NOS) was used for cohort studies. Pooled proportions, odds/risk ratio and 95% confidence intervals of outcomes were obtained and analyzed using the RevMan 5 software [11]. Subgroup analysis for age, SARS-COV-2 PCR result and presence of cardiac dysfunction was planned.

RESULTS

PART 1: Steroid versus IVIg (1 RCT)

Characteristics of included studies

After thorough search, there was one RCT available for review comparing steroid versus IVIg [12]. This study included a total of 75 patients which fulfilled the case definition of the Swiss PIMS-TS as defined by the RCPCH [13] (Appendix 4a). The intervention used was either intravenous methylprednisolone (10mg/kg/dose once a day for three days, maximum of 1,000mg/day) or intravenous immunoglobulin (2g/kg/dose as single dose via slow infusion over 12 ± 4 hours, maximum 100mg/dose). This was an open-label trial which evaluated objective outcomes such as length of hospital stay, mortality, need for and duration of organ support, and presence of serious adverse events [12].

The critical outcomes that were reviewed in this RCT were mortality, need for respiratory support, and presence of serious adverse events. Meanwhile, the important outcomes were as follows: clinical improvement as measured by the patient's length of stay, clinical deterioration as seen in the need for ICU admission, and duration of respiratory support. Respiratory support was defined as use of invasive ventilation, continuous positive airway pressure, biphasic positive airway, and high and low flow supplementary oxygen after randomization.

Efficacy outcomes

Based on the data, the need for respiratory support was significantly decreased in the steroid group versus the IVIg group (RR 0.22, 95% CI 0.05-0.85, very low certainty). The presence of serious adverse events (RR 1.37, 95% CI 0.33-5.70, very low certainty), length of hospital stay (MD -0.5 days, 95% CI -22.4 to 21.4, very low certainty), need for ICU admission (RR 0.77, 95% CI 0.47-1.26, very low certainty), and duration of respiratory support (MD -0.5 days, 95% CI -21.8 to 22.8, very low certainty) were not significantly different between the steroid versus the IVIg group (Table 1 and Appendix 6a). There was no noted mortality in the population examined, hence was not included in the summary of findings.

Table 1. Summary of Findings for Steroid (Methylprednisolone) versus IVIg alone

OUTCOMES	BASIS (Number and Type of Studies, Total Participants)	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIIDENCE
Need for respiratory support post randomization	1 RCT (n=75)	RR 0.22	0.05, 0.85	Benefit (Favors Steroids)	Very Low
Serious adverse events	1 RCT (n=75)	RR 1.37	0.33, 5.70	Inconclusive	Very Low
Length of stay	1 RCT (n=75)	MD -0.5 days	-22.4,21.4	Inconclusive	Very Low
ICU admission	1 RCT (n=75)	RR 0.77	0.47,1.26	Inconclusive	Very Low
Duration of any respiratory support	1 RCT (n=75)	MD -0.5	-21.8,22.8	Inconclusive	Very Low

Safety outcomes

Adverse events noted in the methylprednisolone group include the following: one event with knee pain, abdominal pain, and subfebrile temperature; one event with fever, headache, body ache, and rash; one with hyperglycemia; and one with agitation and lethargy. Among the events, all were non-serious and only two were noted to be possibly related to the investigated medical product: hyperglycemia and agitation and lethargy. For the IVIg group, adverse events were: one case with fever, vomiting, and abdominal pain, one hypotensive shock, and one intracranial thrombi. The last two were serious adverse events however, only hypotensive shock was noted to be possibly related to the investigated medical product [12].

Certainty of evidence

Based on the risk of bias tool, the study had serious risk of bias due to absence of blinding of the participant, personnel, and outcome assessor despite the presence of randomization, allocation concealment, use of intention to treat analysis, absence of selective reporting and adequate follow up (Appendix 5a). In addition, the population recruited did not meet the target sample size due to decline in confirmed MIS-C cases, thus conclusions for the secondary outcomes were underpowered. Publication bias was also suspected since the evidence retrieved came only from a single small study. Due to the above-mentioned reasons, the certainty of evidence was downgraded to very low (Appendix 6a).

PART 2: IVIg plus Steroid versus IVIg alone (7 retrospective cohort studies)

Characteristics of included studies

Despite thorough search, no randomized controlled trial was available for the second part of the review. Seven retrospective cohort studies were included with a total of 1,553 MIS-C patients diagnosed using any of the published criteria. There was noted differences in the characteristics of the patient population in the combined versus IVIg alone group versus the IVIg alone group. The study by Ouldali reported that the patients who received combination treatment had more severe initial presentation, with more frequent initial acute left ventricular dysfunction, ICU care upon admission, and requirement of hemodynamic support upon admission [16]. McArdle showed that patients who received combination therapy had higher troponin levels and had higher need for inotropes upon admission [10]. Harthan reported a high proportion of patients with abnormal inflammatory mediators on day zero or one of admission in the combined group [14]. The mediators were as follows: high or low leukocyte count, platelet, and fibrinogen; high CRP, procalcitonin, ferritin, interleukin, and d-dimer; and low serum albumin [14]. The study by Bagri showed significantly lower mean ejection fraction at baseline and significantly lower platelet counts, and higher CRP and ferritin in the combined group [15]. The study by Devrim noted that higher cases of severe MIS-C, lower platelet and lymphocyte count, and higher CRP in the combined group [19].

All the studies compared IVIg plus steroid with IVIg alone with critical outcomes as follows: all-cause mortality [10,14,15], and need for mechanical ventilator at least 24 hours from initial therapy [10,14]. Important outcomes reviewed were clinical improvement measured by hospital length of stay [14,15,18], clinical deterioration as measured by the need for ICU admission [14,17-19], need for vasopressors at least 24 hours from initial therapy [10,14,16,17], persistence of fever 24 hours after initial therapy [10, 14, 16,17, 19], and need for adjunctive therapy at least 24 hours from initial therapy [10,16,17,18]. The adjunctive therapy used were the following: second dose of IVIg, additional or increased steroid dose, or biologics such as tocilizumab or anakinra. The dose of IVIg used in four studies was 2g/kg [16-19], while the remaining three studies did not specify the IVIg dose. On the other hand, the steroid and dose used by the studies were as follows: Ouldali: methylprednisolone 2mg/kg/day for 5 days or bolus of 15-30mg/kg/day x 3 days [16], Son: methylprednisolone 2mg/kg/day, or dexamethasone 0.3mg/kg/day, or prednisone 2mg/kg/day [17], Devrim and Tagarro: methylprednisolone 2mg/kg/day or equivalent [18,19]. Bagri did not specify the dose of steroid but mentioned using methylprednisolone, or prednisone, or dexamethasone [15], while McArdle and Harhan did not specify the dose and type of steroid used [10,14]. Summary of the study characteristics are tabulated in Appendix 4b.

Efficacy outcomes

Based on the pooled data, there was no significant difference between the combined IVIg + steroid versus IVIg alone in the critical outcomes: reducing mortality (OR 1.72, 95% CI 0.64-4.60, I^2=0%, very low certainty) and in the need for mechanical ventilation (OR 1.69, 95% CI 0.95-3.00, I^2=0%, very low certainty) in children with MIS-C. For the important outcomes, there was no significant difference in the hospital length of stay (MD 0.27 days, 95% CI -6.09-6.63, I^2=0%, very low certainty), need for ICU admission (OR 1.60, 95% CI 0.83-3.06, very low certainty) and need for vasopressors (OR 0.82, 95% CI 0.39-1.73, I^2=65%, very low certainty). Conversely, combined therapy showed significantly reduced persistence of fever (OR 0.58, 95% CI 0.42-0.80, I^2=14%, very low certainty), and reduced need for adjunctive therapy (OR 0.33, 95% CI 0.24-0.45, I^2=0%, very low certainty) compared to IVIg alone. The GRADE summary of outcomes is shown in Table 2 and Appendix 4b and corresponding forest plots in Appendix 5a.

Table 2. Summary of Findings for IVIg plus Steroid vs IVIg alone

OUTCOMES	BASIS (No and Type of Studies, Total Participants)	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIIDENCE
Mortality	3 cohort studies (n=848)	OR 1.72	0.64,4.60	Inconclusive	Very Low
Need for mechanical ventilation	2 cohort studies (n=577)	OR 1.69	0.95, 3.00	Inconclusive	Very Low
Length of stay	3 cohort studies (n=384)	MD 0.27 days	-6.09,6.63	Inconclusive	Very Low
ICU admission	4 cohort studies (n=585)	OR 1.60	0.83,3.06	Inconclusive	Very Low
Need for vasopressors	4 cohort studies (n=971)	OR 0.82	0.39,1.73	Inconclusive	Very Low
Persistence of fever	5 cohort studies (n=930)	OR 0.58	0.42,0.80	Benefit (with IVIg + Steroids)	Very Low
Need for adjunctive therapy	4 cohort studies (n=911)	OR 0.33	0.24,0.45	Benefit (with IVIg + Steroids)	Very Low

One study [16] was able to do subgroup analysis for risk of treatment failure among children younger or older than 10 years old, and those with present or absent ventricular dysfunction on admission. Results revealed that the association of combined therapy in reducing treatment failure is similar in both subgroups (OR 0.17, 95% CI 0.04-0.61, very low certainty). One study followed up patients until after 3 months after admission [16]. No cardiovascular complication or persistent inflammatory syndrome were reported [16].

Safety outcomes

Only one study reported drug related complications [10]. There were a total of 16 reported complications for those given glucocorticoids (16/411, 3.9%): one episode of profound bradycardia, seven episodes of hyperglycemia, seven episodes of hypertension and one unspecified complication. On the other hand, there were 9 complications reported for IVIg (9/508, 1.8%): one episode of mild rash and lip swelling and eight unspecified complications.

Certainty of evidence

Based on the NOS scale for cohort studies, one of the seven articles had good quality evidence [16], while six had poor quality [10,14,15,17, 18, 19]. For the selection domain, two studies have unclear ascertainment of exposure [18,19]. In addition, all of the studies did not demonstrate that outcome of interest was not present at the start of the study. For the comparability domain, only five studies [10,15-18] utilized

propensity score matching, multivariable mixed regression, or inverse probability weighing to reduce confounding bias. Lastly, for the outcome domain, follow up was described in only one study [16], thus the duration and adequacy of the outcome were not assessed. These resulted in poor quality evidence and thus high risk of bias (Appendix 6b).

The overall certainty of evidence for the critical and important outcomes was very low due to the serious risk of bias in study design, inconsistency, and imprecision of outcomes. This can be attributed to the retrospective observational cohort study design, small sample size, presence of selection and confounding bias in most studies.

PART 3: Steroid versus IVIg plus (4 retrospective cohort studies)

Characteristics of included studies

After thorough search, there was no randomized controlled trial available for review. Four retrospective cohort studies were included which investigated the comparison between steroid alone versus the combination of IVIg and steroids. A total of 795 MIS-C patients diagnosed using the CDC or WHO guidelines were utilized. The study by Villacis Nunez reported that the combined group has higher frequency of respiratory, ocular, and cardiovascular involvement than the steroid group [20]. The study by Bagri showed significantly lower mean ejection fraction at baseline and significantly lower platelet counts, and higher CRP and ferritin in the combined group [15]. Meanwhile, the study by Harthan mentioned a high proportion of patients with abnormal inflammatory mediators on day zero or one of admission in the combined group [14]. The mediators are as follows: high or low leukocyte count, platelet, and fibrinogen; high CRP, procalcitonin, ferritin, interleukin, and d-dimer; and low serum albumin [14].

This review investigated the following critical outcomes: all-cause mortality [14,15], need for mechanical ventilation at least 24 hours from initiation of treatment [14]. On the other hand, the important outcomes assessed were clinical improvement measured by hospital length of stay [14,15,18,20], clinical deterioration measured by the need for ICU admission [14,18,20], need for vasopressors at least 24 hours from initiation of treatment [14], persistence of fever at least 24 hours from initiation of treatment [14,20], and need for adjunctive therapy at least 24 hours from initial treatment [18].

The adjunctive therapy used in the study were the following: IVIg and tocilizumab for the steroid group, and IVIg, IVIg+anakinra, anakinra, and tocilizumab for the combined IVIg+steroid group. The type of steroid used was methylprednisolone, prednisone, or dexamethasone in three studies [15,18,20]. In the study by Villacis-Nunez, the dose for methylprednisolone was 10-30mg/kg every 24 hours or a maximum of 1,000mg if patient's weight was more than 35kg, or equivalent dose of prednisone or prednisolone [20]. In the study by Tagarro, the dose of methylprednisolone was 2mg/kg/day or equivalent dose of another steroid [18]. Meanwhile, the dose of methylprednisolone, prednisone, or dexamethasone was not specified in the study by Bagri [15]. Lastly, in the study by Harthan, the dose and type of steroid use was unspecified. For IVIg, two studies used the dose of 2g/kg as single dose [18,20], while it was unspecified in the remaining two studies [14,15]. Summary of the study characteristics are tabulated in Appendix 4c.

Efficacy outcomes

Table 3. Grade Summary of Findings for IVIg plus Steroid vs Steroids alone

OUTCOMES	BASIS (No and Type of Studies, Total Participants)	EFFECT SIZE	95% CI	INTERPRETATION	CERTAINTY OF EVIIDENCE
Mortality	2 cohort studies (n=390)	OR 1.13	0.54, 2.37	Inconclusive	Very Low
Need for mechanical ventilation	1 cohort study (n=153)	OR 3.04	0.78,11.84	Inconclusive	Very Low
Length of stay	4 cohort studies (n=579)	MD -0.54 days	-4.31,3.24	Inconclusive	Very Low
ICU admission	3 cohort studies (n=342)	OR 1.58	0.74,3.34	Inconclusive	Very Low
Need for vasopressors	1 cohort study (n=153)	OR 3.22	0.93,11.13	Inconclusive	Very Low
Persistence of fever	2 cohort studies (n=218)	OR 0.45	0.05, 4.32	Inconclusive	Very Low
Need for adjunctive therapy	1 cohort study (n=73)	OR 1.98	0.74,5.29	Inconclusive	Very Low

For the critical outcomes, there was no significant difference in mortality (OR 1.13, 95% CI 0.54-2.37, I^2=0%, very low certainty) and need for mechanical ventilation (OR 3.04, 95% CI 0.78-11.84, very low certainty) between the steroid only group vs. the combined IVIg plus steroid group based on pooled data. On the other hand, for the important outcomes, there was also no significant difference in the length of hospital stay (MD -0.54 days, 95% CI -4.31 to 3.24, I^2=0%, very low certainty), need for ICU admission (OR 1.58, 95% CI 0.74-3.34, I^2=56%, very low certainty), need for vasopressors (OR 3.22, 95% CI 0.93-11.13, very low certainty), persistence of fever (OR 0.45, 95% CI 0.05-4.32, I^2=78%, very low certainty), and need for adjunctive therapy (OR 1.98, 95% CI 0.74-5.29, very low certainty).

Although the outcomes showed inconclusive results, a trend towards benefit favoring the combined group was seen in the need for ICU admission while a trend towards benefit favoring steroids was seen in persistence of fever. For the other outcomes, although we observed a trend favoring one treatment, they have either low sample size, low event rate, very wide confidence intervals, or effect estimates almost midline.

The GRADE summary of outcomes is shown in Table 3 and Appendix 6c and corresponding forest plots in Appendix 7b.

Safety outcomes

Only one study detailed adverse events potentially related to medications given [20]. Thirteen adverse events were noted in the steroid group: 7 cases of hyperglycemia (10.1%), 2 cases each of hypertension (2.9%), psychosis (2.9%), and gastrointestinal bleeding (2.9%). On the other hand, there were 82 events noted in the combined IVIg plus steroid group: 33 cases of fever during IVIg infusion (31.3%), 28 cases of hyperglycemia (24.3%), 6 cases each of hypertension (5.2%) and gastrointestinal bleeding (5.2%), 4 cases of psychosis (3.5%), 3 cases of aseptic meningitis (2.6%), and 2 cases of hemolytic anemia (1.7%). The only noted serious adverse event was gastrointestinal bleeding.

Certainty of evidence

Based on the NOS scale for cohort studies, all of the four studies had poor quality of evidence and thus have a high risk of bias [14,15,18,20] (Appendix 4c). Only one study was able to provide ascertainment of exposure [14], and none of the studies was able to demonstrate that outcome of interest was not present

at the start of the study. All of the studies used either propensity score matching or multivariable mixed regression to adjust possible confounding factors from the population and thus reduce bias. Lastly, none of the studies conducted a follow up for the participants hence the duration and adequacy of the outcome was not assessed.

The overall certainty of evidence for the critical and important outcomes was assessed to be very low due to serious risk of bias due to the study design, inconsistency, and imprecision of outcomes. This can be attributed to the retrospective observational cohort study design, small sample size, presence of selection and confounding bias in most studies.

RECOMMENDATIONS FROM OTHER GROUPS

Group or Agency/ Last update	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
Australian guidelines for the clinical care of people with COVID 19 [22] Updated April 26, 2023	Children under 5 years • No hemodynamic compromise: Give IVIg 2g/kg/dose – single dose (maximum 100g/dose); AND give intravenous methylprednisolone 2mg/kg/day (maximum 1,000mg/day) for 3 days • With hemodynamic compromise, and/or no/limited improvement with above: Consider the following, in order, until improvement - increase dose of intravenous methylprednisolone 10mg/kg/day (maximum 1,000mg/day) for 3 days - add intravenous immunoglobulin 2g/kg/dose – single dose (maximum 100g/dose) - add biologics anti-IL-1, anti-IL-6 or anti-TNF • If with MIS-C AND Kawasaki disease-like features, give IVIG 2g/kg/dose – single dose (maximum 100g/dose) Children and adolescents 5 years and older • No hemodynamic compromise: Give intravenous methylprednisolone 2mg/kg/day (maximum 1,000mg/day) for 3 days • With hemodynamic compromise, and/or no/limited improvement with above: Consider the following, in order, until improvement: - increase dose of intravenous methylprednisolone 10mg/kg/day (maximum 1,000mg/day) for 3 days - add intravenous immunoglobulin 2g/kg/dose – single dose (maximum 100g/dose) - add biologics anti-IL-1, anti-IL-6 or anti-TNF • If with MIS-C AND Kawasaki disease-like features, give IVIg 2g/kg/dose – single dose (maximum 100g/dose) and intravenous	Consensus recommendation

	methylprednisolone as initial therapy, doses as above	
World Health Organization [21] Updated January 13, 2023	Hospitalized children aged 0-18 • Standard case definition for MIS-C: we suggest using corticosteroids in addition to supportive care (rather than either IVIg plus supportive care or supportive care alone) Both standard case definition for MIS-C and diagnostic criteria for Kawasaki disease: we suggest using corticosteroids in addition to standard of care for Kawasaki disease	Conditional recommendation, very low certainty
National Institutes of Health [23] Updated December 28, 2022	IVIG 2g/kg IBW/dose (up to a maximum total dose of 100g) IV plus low-to-moderate dose methylprednisolone (1-2mg/kg/day) IV or another glucocorticoid at an equivalent dose	Strong recommendation, moderate quality of evidence
American College of Rheumatology [26] Updated February 3, 2022	IVIg 2mg/kg and methylprednisolone IV 1-2mg/kg/day as first-tier therapy in most hospitalized patients	Moderate level of consensus
Philippine Pediatric Society [24] Updated January 8, 2022	Methylprednisolone 1-2mg/kg/dose (maximum 30mg/dose) IV q12 initially then shift to PO once afebrile or after 3-5 days, then taper off over 3-4 weeks OR IVIg 2g/lg over 8-12 hours (maximum 100g) + Corticosteroids	Rapid review
Government of India Ministry of Health and Family Welfare [25] Updated January 2022	MIS-C with shock or MODS • IVIg 2g/kg over 12-16 hours (maximum 100g) and IV methylprednisolone 2mg/kg/day and empirical antibiotics as per hospital antibiogram MIS-C with Kawasaki phenotype • IVIG 2g/kg over 12-16 hours (maximum 100g) and IV methylprednisolone 1-2 mg/kg/day MIS-C without shock • IV methylprednisolone 1-2mg/kg/day	Consensus of experts
Best Practice Recommendations in Switzerland [27] Published May 26, 2021	Kawasaki-like MIS-C • IVIG 2g/kg (max 100g) single dose • *Consider* prednisolone 2mg/kg/day (max 60mg) in children with coronary artery dilatation/aneurysms, high risk for IVIG resistance, or under 1 year old MIS-C undefined inflammatory presentation • IVIG 2g/kg (max 100g) single dose • Prednisolone 2mg/kg/day (max 60mg) with slow wean • Low-dose aspirin 3-5mg/kg/day, (max 100mg) but hold if plt <80 G/L	Consensus of experts

United Kingdom National Consensus Management Pathway [28] Updated January 20, 2021	IVIg 2 g/kg, calculated using ideal bodyweight, in a single or divided dose depending on the clinical picture and cardiac function	Consensus of experts

ONGOING STUDIES AND RESEARCH GAPS

There is one ongoing study involving IVIg and methylprednisolone in children with MIS-C as of May 4, 2023 as listed in Appendix 8. This is an open label multi-arm randomized controlled trial which will compare patients treated with IVIg with either infliximab, anakinra, or methylprednisolone. The target date of completion is on December 23, 2023 [29].

There is lack of consensus among organizations regarding MIS-C treatment in children. Various management recommendations depending on age, clinical presentation, and disease severity were presented but all of which lack strong evidence. This highlights the need for randomized controlled trials to assess the efficacy of treatment.

ADDITIONAL CONSIDERATIONS FOR EVIDENCE TO DECISION (ETD) PHASE

COST

There are no studies on cost effectiveness of IVIG and steroids in MIS-C as of May 4, 2023. The local cost of each intervention was retrieved from the Drug Price Reference Index by the Department of Health [30] (Table 5; Appendix 9).

Table 5. Drug price of interventions

	Immunoglobulin	Methylprednisolone
Recommended dose based on PPS [13]	2g/kg over 8-12 hours (max dose 100g)	2 mg/kg/day (max 30mg/dose) x 3 days
Drug preparation	Normal, Human (IVIg) 50mg/mL, 100mL vial	40mg (single dose) vial
Cost per preparation based on 2022 DRPI	₱15,800	₱716.85
Sample cost of initial treatment for a 10kg child	4 vials = ₱63,200	6 vials = ₱4,301.10
Total cost of initial treatment for a 10kg child	₱67,501.10	

PATIENT'S VALUES AND PREFERENCE, EQUITY, ACCEPTABILITY, AND FEASIBILITY

As of May 4, 2023, there are no studies on patient's values and preference, equity, acceptability, feasibility, or compliance with IVIg and steroids in children with MIS-C.

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Appendix 1: Preliminary Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=8/10)

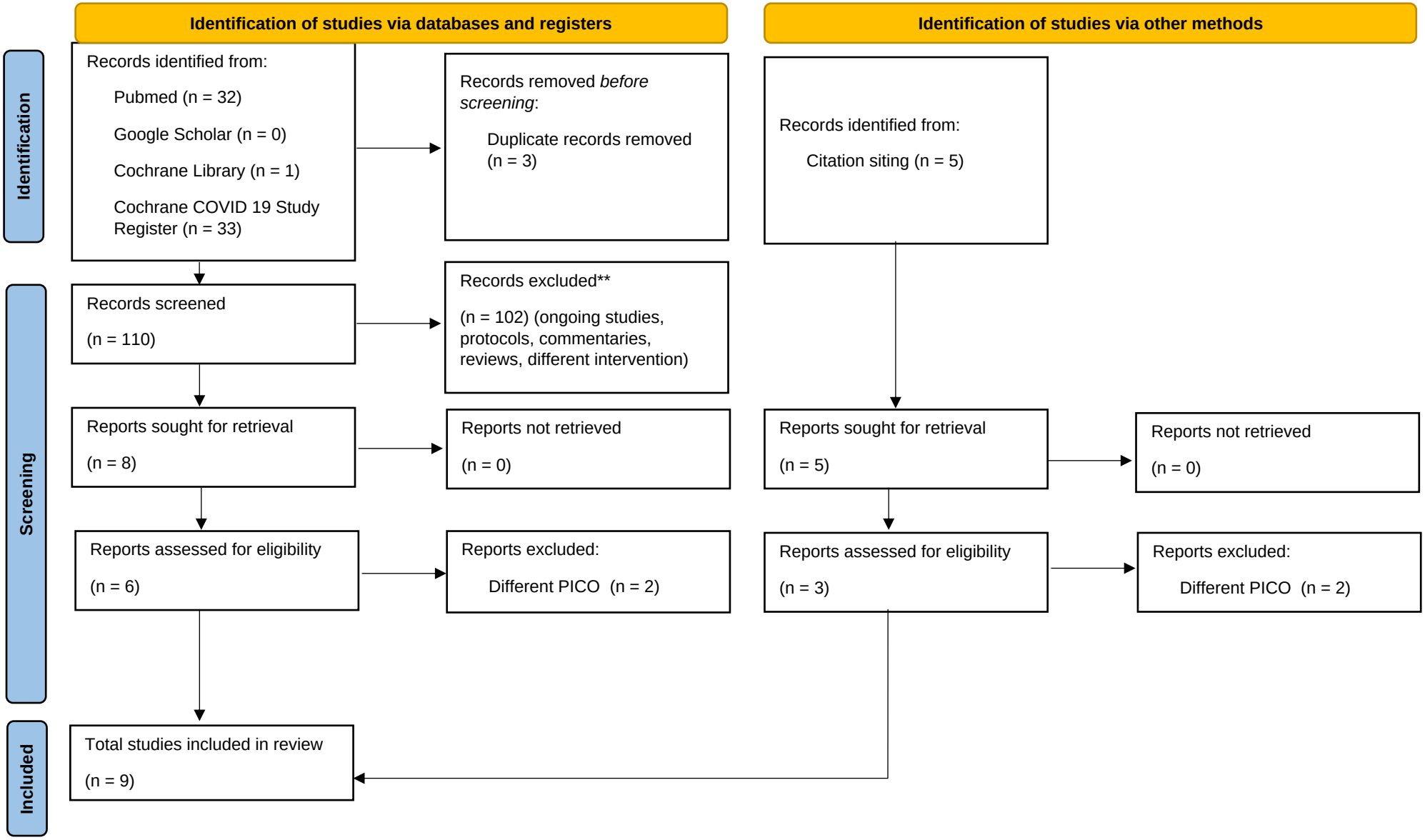
FACTORS	JUDGEMENT				RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (7)	Varies (1)		Multisystem inflammatory syndrome in children (MIS-C) is a rare but serious complication of severe acute respiratory coronavirus 2 (SARS-CoV-2) first described in April 2020 [1-5] Currently, there is insufficient evidence to support the use of any of the suggested treatment strategies.
Benefits	Large (1)	Moderate (4)	Small (2)	Trivial (1)	**Steroid vs IVIg+Steroid**: For the critical outcomes, there is **no significant difference in mortality (OR 1.13, 95% CI 0.54-2.37, I^2=0%, very low certainty)** and need for mechanical ventilation (OR 3.04, 95% CI 0.78-11.84, very low certainty) between the steroid only group vs the combined IVIg plus steroid group based on pooled data.
Harm	Large	Moderate (3)	Small (4)	Trivial (1)	**IVIg vs steroid**: 4 patients had non serious adverse events in the methylprednisolone group. For the IVIg group***, one case with non-serious adverse event and two serious adverse events*** (hypotensive shock, and intracranial thrombi). Only hypotensive shock was noted to be possibly related to the investigated medical product [12]. **IVIg+steroid vs IVIg**: There was ***one serious complication among patients given glucocorticoids*** (profound bradycardia), while the others were non serious (hyperglycemia, and hypertension) ***IVIg: (mild rash and lip swelling) was non-serious.***
Certainty of Evidence	High	Moderate	Low	Very low (8)	Presence of serious risk of bias due to lack of blinding in the patients, caregivers, and outcome assessors, low sample size, and use of a single small study; imprecision and inconsistency
Balance of effects	Favors treatment (2)	Probably favors treatment (5)	Probably favors no treatment (2)		There is very low certainty of evidence to suggest the use of steroid (methylprednisolone) or combined IVIg and steroid for children diagnosed with MIS-C. There is significant reduction in need for respiratory support in patients given methylprednisolone and significantly less persistent fever and reduced need

								for adjunctive therapy in patients given combination IVIg+ steroid versus IVIg alone.
Values	Important uncertainty or variability (3)		Possibly important uncertainty or variability (2)	Possibly NO important uncertainty or variability (3)	No important uncertainty or variability			
Resources Required	Uncertain	Varies	Large cost (4)	Moderate cost (4)	Negligible cost	Moderate savings	Large savings	A 5g vial of IVIg costs ₱9,500 while a 40mg vial of methylprednisolone costs ₱289.95. In a 10kg child with MIS-C, cost of treatment if using the dose recommended by PPS will be the following: **methylprednisolone only ₱1,730.70; IVIg only ₱38,000; and if combined IVIg+ methylprednisolone ₱39,739.70.**
Certainty of evidence of required resources	No included studies (3)		Very low	Low (2)	Moderate (3)	High		
Cost effectiveness	No included studies (3)		Probably favors the comparison (2)	Probably favors the intervention (2)	Favors the intervention (1)	Varies		There are no studies on cost effectiveness of IVIg or steroids in MIS-C. (The price of IVIg is almost 19x greater than the price of methylprednisolone).
Equity	Varies (3)	Reduced (1)	Probably reduced	Probably no impact (1)	Probably increased (1)	Uncertain (2)		
Acceptability	Varies (1)		No	Probably no (1)	Yes (1)	Probably yes (5)		**<u>For the use: 7 (weak)</u>** **<u>Against the use: 1</u>** **While there are no cost-effectiveness studies on the use of IVIg and steroids, it may be worth administering to the patient due to the risk/severity of the illness.*
Feasibility	Varies (1)		No	Probably no (1)	Yes	Probably yes (6)		

Appendix 2: Search Strategy and Yield

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Pubmed	Search: (("pediatric multisystem inflammatory disease, COVID-19 related" [Supplementary Concept]) AND "Immunoglobulins, Intravenous"[Mesh]) AND "Steroids"[Mesh] Sort by: Most Recent	May 4, 2023 10:09 PM	32	6
COVID-NMA Initiative	Intravenous immunoglobulin and steroid	May 4, 2023 10:30 PM	0	0
Cochrane Library	MIS-C intravenous immunoglobulin steroid	May 4, 2023 11:01 PM	1	0
Google Scholar	allintitle: steroids intravenous immunoglobulin MIS-C	May 4, 2023 10: 40 PM	0	0
ClinicalTrials.gov	MIS-C IVIg steroid	May 4, 2023 11:15 PM	2	0
Chinese Clinical Trial Registry	MIS-C	May 4, 2023 11: 20 PM	0	0
EU Clinical Trials Register	PIMS-TS IVIg steroid	May 4, 2023 11:32 PM	0	0
Republic of Korea - Clinical Research Information Service	MIS-C IVIg steroid	May 4, 2023 11:35 PM	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	MIS-C intravenous immunoglobulin steroid	May 4, 2023 11:40 PM	0	0
CenterWatch	MIS-C	May 4, 2023 11:44 PM	9	0
Cochrane COVID-19 study register	MIS-C IVIg steroid	May 4, 2023 11:48 PM	33	1
chinaxiv.org	MIS-C intravenous immunoglobulin steroid	May 4, 2023 11:49 PM	0	0
Medrxiv.org	MIS-C and intravenous immunoglobulin steroids	May 4, 2023 11:50 PM	33	0
Biorxiv.org	MIS-C and intravenous immunoglobulin steroids	May 4, 2023 11:53 PM	3	0

Appendix 3: PRISMA Flow Diagram



Appendix 4a: Characteristics of Included Studies for Part 1

Study ID Title Author	Study Design	Setting/ Country	Total number of Patients Included	Population	Intervention	Comparator/ Control	Outcomes
Methylprednisolone versus intravenous immunoglobulins in children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS): an open-label, multicentre, randomised trial Welzel et. al. (2023) PMID: 36746174	Randomized controlled trial	Switzerland	N=75 I: 37 C: 38	Children younger than 18 years old hospitalized with PIMS-TS Age range: 44 weeks to 18 years old	Intravenous methylprednisolone (10mg/kg/day) x 3 days Median age (yrs/IQR): 8.9 (6.2-12.9)	IVIg 2g/kg as single dose Median age: 9.4 (6.8-11.6)	Primary outcome: Length of hospital stay (Time in days from hospital admission to discharge or death, with censoring at 28 days) Secondary outcomes: 1. All-cause mortality 2. Proportion of patients needing organ support (respiratory, inotropes, renal replacement and ECMO) 3. Duration of organ support 4. Proportion of patients with cardiac pathologies

Appendix 4b: Characteristics of Included Studies for Part 2

Study ID Title Author	Study Design	Setting/ Country	Total number of Patients Included	Population	Intervention	Comparator/ Control	Outcomes
Association of Intravenous Immunoglobulins Plus Methylprednisolone vs Immunoglobulins Alone With Course of Fever in Multisystem Inflammatory Syndrome in Children Ouldali et. al. (2021) PMID: 33523115	Retrospective cohort	France	N=106 I: 34 C: 72	Children and adolescents 0-19 years old with confirmed MIS-C associated with SARS-CoV-2 infection fulfilling WHO criteria Age range: 0-19 yrs	IVIG 2g/kg + methylprednisolone [0.8-1 mg/kg every 12 hours (max of 30mg for 12 hours) for 5 days] or bolus of 15-30mg/kg/day x 3 days Median age (yrs/IQR): 9.1 (4.7-13.1)	IVIg 2g/kg Median age (yrs/IQR): 8.7 (4.6-12)	Primary outcome: Treatment failure (persistence of fever for 2 days after introduction of initial therapy or recrudescence of fever within 7 days after initial therapy) Secondary outcomes: 1. Second-line therapy 2. Hemodynamic support 3. Occurrence of acute left ventricular dysfunction 4. Duration of stay in PICU
Treatment of Multisystem Inflammatory Syndrome in Children McArdle et. al. (2021) PMID: 34133854	Observational cohort	Worldwide	N= 454 I: 208 C: 246	Children who met the published criteria for MIS-C and any suspected illness after SARS-CoV2 infection Age range: 0-21 yrs	IVIG plus glucocorticoids (Dose and type of steroid not specified) Median age (yrs/IQR): 8.8 (4.6-12)	IVIg (Dose not specified) Median age (yrs/IQR): 7 (3.7-11)	Primary outcome: 1. Inotropic support or mechanical ventilation by day 2 or later or death 2. Reduction in disease severity on a seven-point ordinal scale between day 0 and day 2 Secondary outcomes: 1. Temporal dynamics of blood markers of inflammation and organ damage 2. Escalation in the administration of immunomodulators 3. Time until a reduction of 1 point in disease severity in the ordinal scale 4. Left ventricular dysfunction on echo 5. Coronary artery aneurysm after treatment 6. Any increase in cardiorespiratory supportive therapy after day 0 7. Other therapeutic complications or death

Study ID Title Author	Study Design	Setting/ Country	Total number of Patients Included	Population	Intervention	Comparator/ Control	Outcomes
Multisystem Inflammatory Syndrome in Children - Initial Therapy and Outcomes Son et. al. (2021) PMID: 34133855	Observational cohort	USA	N=349 I: 157 C: 192	Inpatients younger than 21 years old who had MIS-C fulfilling the CDC criteria Age range: 0-21 yrs	IVIG 2g/kg + glucocorticoids (Methylprednisolone 2mg/kg/day OR dexamethasone 0.3 mg/kg/day OR prednisone 2mg/kg/day) Median age (yrs/IQR): 8.6 (4.6-12)	IVIG 2g/kg Median age (yrs/IQR): 5.5 (2.5-10.5)	Primary outcome: Cardiovascular dysfunction on or after day 2 to discharge Secondary outcomes 1. Receipt of adjunctive immunomodulatory treatment after day 1 2. Persistent or recurrent fever on or after day 2 3. Length of stay in ICU
Early combination therapy with immunoglobulin and steroids is associated with shorter ICU length of stay in Multisystem Inflammatory Syndrome in Children (MIS-C) associated with COVID-19: A retrospective cohort analysis from 28 U.S. Hospitals Harthan et. al. (2022) PMID: 35661394	Retrospective cohort	USA	N=186 I: 153 C: 33	Pediatric patients <18 years old diagnosed with MIS-C using CDC criteria Age range: 0-18 yrs	IVIG + steroids (Dose and type of steroid not specified) Median age (yrs/IQR): 8.9 (5.5-12)	IVIG (Dose not specified) Median age (yrs/IQR): 5.5 (3.4-11)	Primary outcome: Hospital and ICU length of stay Secondary outcomes: 1. Hospital mortality 2. Nosocomial bacterial infection 3. Inotrope or ventilator requirement on or after hospital day 2 4. Number of days on inotropes 5. Fever defervescense by day 3 6. Day of normalization of inflammatory markers
Initial Immunomodulation and Outcome of Children with Multisystem Inflammatory Syndrome Related to COVID-19: A Multisite Study from India Bagri et. al. (2022)	Retrospective cohort	India	N=265 I: 237 C: 28	Children meeting the WHO case definition for MIS-C Age range: 0-19 yrs	IVIG + steroids [Dose not specified (methylprednisolone OR prednisone OR dexamethasone)] Median age (yrs/IQR): 7 (4-6.25)	IVIG (Dose not specified) Median age (yrs/IQR): 4.25 (1.2-7)	Requirement of vasoactive/inotropic support on day 2 or beyond after initiation of therapy or need for mechanical ventilation on day 2 or beyond after initiation of therapy or death during hospitalization

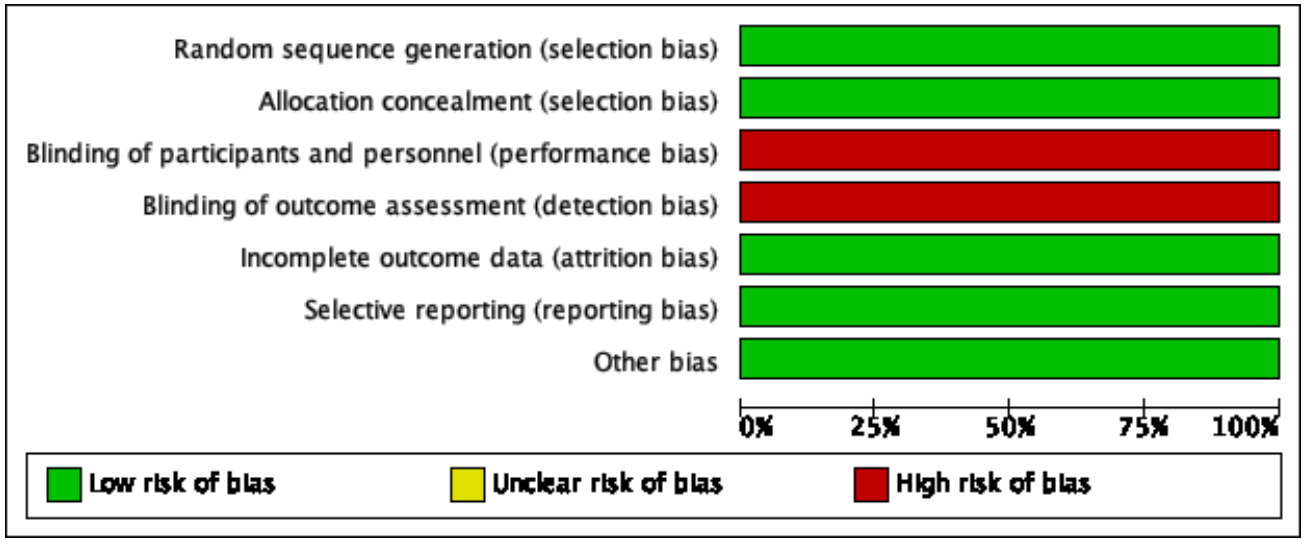
Study ID Title Author	Study Design	Setting/ Country	Total number of Patients Included	Population	Intervention	Comparator/ Control	Outcomes
A retrospective comparative analysis of factors affecting the decision and outcome of initial intravenous immunoglobulin alone or intravenous immunoglobulin plus methylprednisolone use in children with the multisystem inflammatory syndrome Devrim et. al. (2022)	Retrospective cohort	Turkey	N=91 I: 49 C: 42	Children identified as having MIS-C in accordance to CDC guidelines Age range: 0-21 yrs	IVIG 2g/kg + methylprednisolone 2mg/kg/day Median age (yrs/range): 8 (5mos-14)	IVIG 2g/kg Median age (yrs/range): 4.3 (1.3-17)	1. Frequency of fever 2. Length of hospital stay 3. Admission to the pediatric intensive care unit
Treatments for multi-system inflammatory syndrome in children – discharge, fever, and second-line therapies Tagarro et. al. (2022) PMID: 36282324	Retrospective	Spain	N=102 I: 73 C: 29	Children with MIS-C based on the WHO definition Age range: 0-19 yrs	IVIG 2g/kg + methylprednisolone 2mg/kg/day or equivalent Median age (yrs/IQR): 7.6 (4.1-8.4)	IVIG 2g/kg Median age (yrs/IQR): 9.2 (5.9-12.6)	1. Probability of discharge over time 2. Probability of switching to second-line treatment over time 3. Persistence of fever 2 days after treatment

Appendix 4c: Characteristics of Included Studies for Part 3

Study ID Title Author	Study Design	Setting/ Country	Total number of Patients Included	Population	Intervention	Comparator/ Control	Outcomes
Early combination therapy with immunoglobulin and steroids is associated with shorter ICU length of stay in Multisystem Inflammatory Syndrome in Children (MIS-C) associated with COVID-19: A retrospective cohort analysis from 28 U.S. Hospitals Harthan et. al. (2022) PMID: 35661394	Retrospective cohort	USA	N=196 I: 43 C: 153	Pediatric patients <18 years old diagnosed with MIS-C using CDC criteria Age range: 0-18 yrs	Steroids (Dose and type unspecified) Median age (yrs/IQR): 10 (5.3-15)	IVIG + steroids (Dose not specified) Median age (yrs/IQR): 8.9 (5.5-12)	Primary outcome: Hospital and ICU length of stay Secondary outcomes: 1. Hospital mortality 2. Nosocomial bacterial infection 3. Inotrope or ventilator requirement on or after hospital day 2 4. Number of days on inotropes 5. Fever defervescense by day 3 6. Day of normalization of inflammatory markers
Initial Immunomodulation and Outcome of Children with Multisystem Inflammatory Syndrome Related to COVID-19: A Multisite Study from India Bagri et. al. (2022)	Retrospective cohort	India	N=319 I: 82 C: 237	Children meeting the WHO case definition for MIS-C Age range: 0-19 yrs	Steroid [Dose unspecified (methylprednisolone OR prednisone OR dexamethasone)] Median age (yrs/IQR): 6.7 (2.5-11)	IVIG + steroids [Dose unspecified (methylprednisolone OR prednisone OR dexamethasone)] Median age (yrs/IQR): 7 (4-6.25)	Requirement of vasoactive/inotropic support on day 2 or beyond after initiation of therapy or need for mechanical ventilation on day 2 or beyond after initiation of therapy or death during hospitalization

Study ID Title Author	Study Design	Setting/ Country	Total number of Patients Included	Population	Intervention	Comparator/ Control	Outcomes
Short-term Outcomes of Corticosteroid Monotherapy in Multisystem Inflammatory Syndrome in Children Villacis-Nunez et. al (2022) PMID: 35344042	Retrospective cohort	USA	N=177 I: 61 C: 116	Patients in a tertiary-care pediatric hospital system who had MIS-C per the Centers for Disease Control and Prevention case definition Age range 0-21	Steroid (Methylprednisolone 10-30mg/kg every 24hours or equivalent dose of prednisone/prednisolone) Median age (yrs/IQR): 10 (6-14)	Steroid+IVIg IVIg 2g/kg Median age (yrs/IQR): 8 (5-12)	Primary outcome: Failure of initial therapy Secondary outcomes: 1. Presence of complications 2. Cardiovascular outcomes 3. Fever duration 4. Length of hospital stay and ICU stay 5. Corticosteroid duration 6. Readmission within 6 months of diagnosis
Treatments for multi-system inflammatory syndrome in children – discharge, fever, and second-line therapies Tagarro et. al. (2022) PMID: 36282324	Retrospective	Spain	N=103 I: 30 C: 73	Children with MIS-C based on the WHO definition Age range: 0-19 yrs	Steroid (Methylprednisolone 2mg/kg/day or equivalent) Median age (yrs/IQR): 10.1 (7.1-9.2)	IVIG 2g/kg + methylprednisolone 2mg/kg/day or equivalent Median age (yrs/IQR): 7.6 (4.1-8.4)	1. Probability of discharge over time 2. Probability of switching to second-line treatment over time 3. Persistence of fever 2 days after treatment

Appendix 5a: Risk of Bias Assessment of Included Studies for Part 1



Appendix 5b: Study Appraisal using the NewCastle-Ottawa Scale for Cohort Studies for Parts 2 and 3

Domain	Selection				Comparability	Outcome			Quality
Question	Representativeness of the exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not presented at start of the study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up cohorts	
Ouldali et al. 2021	X	X	X	0	X	X	X	0	GOOD
McArdle et al. 2021	X	X	X	0	X	X	0	0	POOR
Son et al. 2021	X	X	X	0	X	X	0	0	POOR
Harthan et al. 2022	X	X	X	0	X	X	0	0	POOR
Bagri et al. 2022	X	X	0	0	X	X	0	0	POOR
Villacis-Nunez et al. 2022	X	X	0	0	X	X	0	0	POOR
Devrim et al. 2022	X	X	0	0	0	X	0	0	POOR
Tagarro et al. 2022	X	X	0	0	X	X	0	0	POOR

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor)**:**
Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

Appendix 6a: GRADE Evidence Profile table for Part 1

Author(s): Leslie Anne M. del Barrio, MD
Question: Steroid compared to IVIg for MIS-C
Setting: In-patient
Bibliography: Welzel T, Atkinson A, Schöbi N, Andre MC, Bailey DG, Blanchard-Rohner G, Buettcher M, Grazioli S, Koehler H, Perez MH, Trück J. Methylprednisolone versus intravenous immunoglobulins in children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS): an open-label, multicentre, randomised trial. The Lancet Child & Adolescent Health. 2023 Feb 3.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Steroid	IVIg	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	0/37 (0.0%)	0/38 (0.0%)	not estimable		⨁⨁⨁◯ Moderate	CRITICAL
Need for respiratory support after randomization												
1	randomised trials	serious [a]	not serious	not serious	not serious	none	3/37 (8.1%)	11/38 (28.9%)	**RR 0.28** (0.07 to 0.89)	**208 fewer per 1,000** (from 269 fewer to 32 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Serious adverse events												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	publication bias strongly suspected [c]	4/37 (10.8%)	3/38 (7.9%)	**RR 1.37** (0.33 to 5.70)	**29 more per 1,000** (from 53 fewer to 371 more)	⨁◯◯◯ Very low	CRITICAL
Length of stay												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	publication bias strongly suspected [c]	37	38	-	MD **0.5 lower** (22.4 lower to 21.4 higher)	⨁◯◯◯ Very low	IMPORTANT
ICU admission												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	publication bias strongly suspected [c]	15/37 (40.5%)	20/38 (52.6%)	**RR 0.77** (0.47 to 1.26)	**121 fewer per 1,000** (from 279 fewer to 137 more)	⨁◯◯◯ Very low	IMPORTANT
Duration of any respiratory support												
1	randomised trials	serious [a]	not serious	not serious	serious [b]	publication bias strongly suspected [c]	37	38	-	MD **0.5 higher** (21.8 lower to 22.8 higher)	⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations
a. Lack of blinding of participants and personnel (performance bias), and outcome assessment (detection bias)
b. Low sample size
c. Small single study; Evidence was from a relatively recent intervention where early positive findings maybe available but there has not been sufficient time for publication of negative or equivocal result or replication

Appendix 6b: GRADE Evidence Profile table for Part 2

Author(s): Leslie Anne M. del Barrio, MD
Question: IVIg + steroid compared to IVIg alone for children diagnosed with MIS-C?
Setting: In-patient
Bibliography: 1. Ouldali N, Toubiana J, Antona D, Javouhey E, Madhi F, Lorrot M, Léger PL, Galeotti C, Claude C, Wiedemann A, Lachaume N. Association of intravenous immunoglobulins plus methylprednisolone vs immunoglobulins alone with course of fever in multisystem inflammatory syndrome in children. Jama. 2021 Mar 2;325(9):855-64.2. McArdle AJ, Vito O, Patel H, Seaby EG, Shah P, Wilson C, Broderick C, Nijman R, Tremoulet AH, Munblit D, Ulloa-Gutierrez R. Treatment of multisystem inflammatory syndrome in children. New England Journal of Medicine. 2021 Jul 1;385(1):11-22.3. Son MB, Murray N, Friedman K, Young CC, Newhams MM, Feldstein LR, Loftis LL, Tarquinio KM, Singh AR, Heidemann SM, Soma VL. Multisystem inflammatory syndrome in children—initial therapy and outcomes. New England Journal of Medicine. 2021 Jul 1;385(1):23-34.4. Harthan AA, Nadiger M, McGarvey JS, Hanson K, Gharpure VP, Bjornstad EC, Chiotos K, Miller AS, Reikoff RA, Gajic O, Kumar V. Early combination therapy with immunoglobulin and steroids is associated with shorter ICU length of stay in Multisystem Inflammatory Syndrome in Children (MIS-C) associated with COVID-19: A retrospective cohort analysis from 28 US Hospitals. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2022 Jul;42(7):529-39.5. Bagri NK, Khan M, Pandey RM, Lodha R, Kabra SK. Initial immunomodulation and outcome of children with multisystem inflammatory syndrome related to COVID-19: a multisite study from India. Indian Journal of Pediatrics. 2022 Jun 14:1-7.6. Devrim İ, Böncüoğlu E, Kıymet E, Şahinkaya Ş, Çelebi MY, Cem E, Düzgöl M, Arıkan KÖ, Kara AA, Besin D, Vuran G. A retrospective comparative analysis of factors affecting the decision and outcome of initial intravenous immunoglobulin alone or intravenous immunoglobulin plus methylprednisolone use in children with the multisystem inflammatory syndrome. Pediatric Rheumatology. 2022 Aug 20;20(1):69.7. Tagarro A, Domínguez-Rodríguez S, Mesa JM, Epalza C, Grasa C, Iglesias-Bouzas MI, Fernández-Cooke E, Calvo C, Villaverde S, Torres-Fernández D, Méndez-Echevarria A. Treatments for multi-system inflammatory syndrome in children—discharge, fever, and second-line therapies. European Journal of Pediatrics. 2022 Oct 25:1-6.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IVIg + steroid	IVIg alone	Relative (95% CI)	Absolute (95% CI)		
Mortality												
3	observational studies	serious [a]	not serious	not serious	serious[b]	none	34/574 (5.9%)	5/274 (1.8%)	**OR 1.72** (0.64 to 4.60)	**13 more per 1,000** (from 6 fewer to 61 more)	⨁◯◯◯ Very low	CRITICAL
Need for mechanical ventilator												
2	observational studies	serious [a]	not serious	not serious	serious[b]	none	35/336 (10.4%)	22/241 (9.1%)	**OR 1.69** (0.95 to 3.00)	**54 more per 1,000** (from 4 fewer to 140 more)	⨁◯◯◯ Very low	CRITICAL
Length of stay												
3	observational studies	serious [a]	not serious	not serious	serious[b]	none	463	90	-	MD **0.27 higher** (6.09 lower to 6.63 higher)	⨁◯◯◯ Very low	IMPORTANT
Need for ICU admission												
4	observational studies	very serious [a]	serious[c]	not serious	serious[b]	none	244/378 (64.6%)	111/207 (53.6%)	**OR 1.60** (0.83 to 3.06)	**113 more per 1,000** (from 47 fewer to 243 more)	⨁◯◯◯ Very low	IMPORTANT
Need for vasopressors												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IVIg + steroid	IVIg alone	Relative (95% CI)	Absolute (95% CI)		
4	observational studies	serious [a]	serious[c]	not serious	serious[b]	none	78/505 (15.4%)	85/466 (18.2%)	**OR 0.82** (0.39 to 1.73)	**28 fewer per 1,000** (from 102 fewer to 96 more)	⨁◯◯◯ Very low	IMPORTANT
Persistence of fever												
5	observational studies	very serious [a]	not serious	not serious	not serious	none	136/463 (29.4%)	199/467 (42.6%)	**OR 0.58** (0.42 to 0.80)	**125 fewer per 1,000** (from 188 fewer to 53 fewer)	⨁◯◯◯ Very low	IMPORTANT
Need for adjunctive therapy												
4	observational studies	serious [a]	not serious	not serious	not serious	none	100/514 (19.5%)	177/397 (44.6%)	**OR 0.33** (0.24 to 0.45)	**236 fewer per 1,000** (from 284 fewer to 180 fewer)	⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

Explanations

a. Selection and confounding bias
b. Wide confidence interval
c. High heterogeneity

Appendix 6c. GRADE Evidence Profile table for Part 3

Author(s): Leslie Anne M. del Barrio, MD
Question: Steroid compared to IVIg+steroids for MIS-C
Setting: In-patient
Bibliography: [14] Harthan AA, Nadiger M, McGarvey JS, Hanson K, Gharpure VP, Bjornstad EC, Chiotos K, Miller AS, Reikoff RA, Gajic O, Kumar V. Early combination therapy with immunoglobulin and steroids is associated with shorter ICU length of stay in Multisystem Inflammatory Syndrome in Children (MIS-C) associated with COVID-19: A retrospective cohort analysis from 28 US Hospitals. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2022 Jul;42(7):529-39. [15]Bagri NK, Khan M, Pandey RM, Lodha R, Kabra SK. Initial immunomodulation and outcome of children with multisystem inflammatory syndrome related to COVID-19: a multisite study from India. Indian Journal of Pediatrics. 2022 Jun 14:1-7. [30] Villacis-Nunez DS, Jones K, Jabbar A, Fan L, Moore W, Peter AS, Henderson M, Xiang Y, Kelleman MS, Sherry W, Chandrakasan S. Short-term outcomes of corticosteroid monotherapy in multisystem inflammatory syndrome in children. JAMA pediatrics. 2022 Jun 1;176(6):576-84. [18] Tagarro A, Domínguez-Rodríguez S, Mesa JM, Epalza C, Grasa C, Iglesias-Bouzas MI, Fernández-Cooke E, Calvo C, Villaverde S, Torres-Fernández D, Méndez-Echevarria A. Treatments for multi-system inflammatory syndrome in children—discharge, fever, and second-line therapies. European Journal of Pediatrics. 2022 Oct 25:1-6.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	steroid	IVIg+steroids	Relative (95% CI)	Absolute (95% CI)		
Mortality												
2	observational studies	serious [a]	not serious	not serious	not serious	none	11/125 (8.8%)	29/390 (7.4%)	**OR 1.13** (0.54 to 2.37)	**9 more per 1,000** (from 33 fewer to 86 more)	⨁◯◯◯ Very low	CRITICAL
Need for Mechanical Ventilation												
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	4/43 (9.3%)	5/153 (3.3%)	**OR 3.04** (0.78 to 11.84)	**60 more per 1,000** (from 7 fewer to 253 more)	⨁◯◯◯ Very low	CRITICAL
Length of Stay												
4	observational studies	serious [a]	not serious	not serious	serious [b]	none	216	579	-	MD **0.54 lower** (4.31 lower to 3.24 higher)	⨁◯◯◯ Very low	IMPORTANT
Need for ICU admission												
3	observational studies	serious [a]	serious [c]	not serious	not serious	none	94/134 (70.1%)	225/342 (65.8%)	**OR 1.58** (0.74 to 3.34)	**94 more per 1,000** (from 71 fewer to 207 more)	⨁◯◯◯ Very low	IMPORTANT
Need for vasopressors												
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	5/43 (11.6%)	6/153 (3.9%)	**OR 3.22** (0.93 to 11.13)	**77 more per 1,000** (from 3 fewer to 273 more)	⨁◯◯◯ Very low	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	steroid	IVIg+steroids	Relative (95% CI)	Absolute (95% CI)		
Persistence of fever												
2	observational studies	serious [a]	serious[c]	not serious	serious[b]	none	16/89 (18.0%)	50/218 (22.9%)	**OR 0.45** (0.05 to 4.32)	**111 fewer per 1,000** (from 215 fewer to 333 more)	⨁◯◯◯ Very low	IMPORTANT
Need for adjunctive therapy												
1	observational studies	serious [a]	not serious	not serious	serious[b]	none	9/30 (30.0%)	13/73 (17.8%)	**OR 1.98** (0.74 to 5.29)	**122 more per 1,000** (from 40 fewer to 356 more)	⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

Explanations

a. Selection and confounding bias
b. Wide confidence interval
c. High heterogeneity

Appendix 7a: Forest plots for studies comparing IVIg + Steroids (Methylprednisolone) versus IVIg Alone

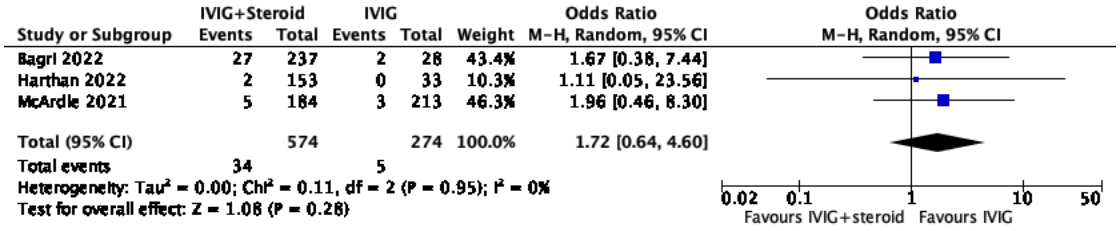


Figure 1. Comparing mortality between IVIG + steroids vs IVIG alone

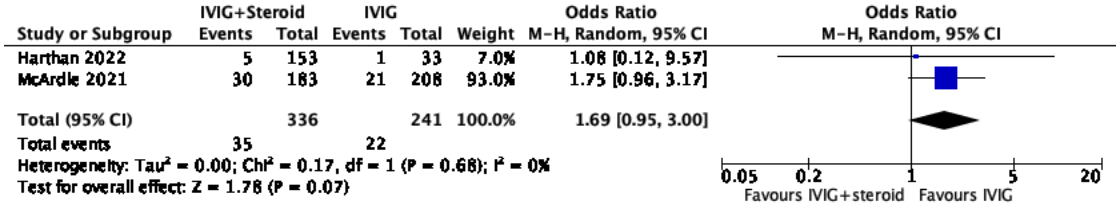


Figure 2. Comparing the need for mechanical ventilation between IVIG + steroids vs IVIG alone

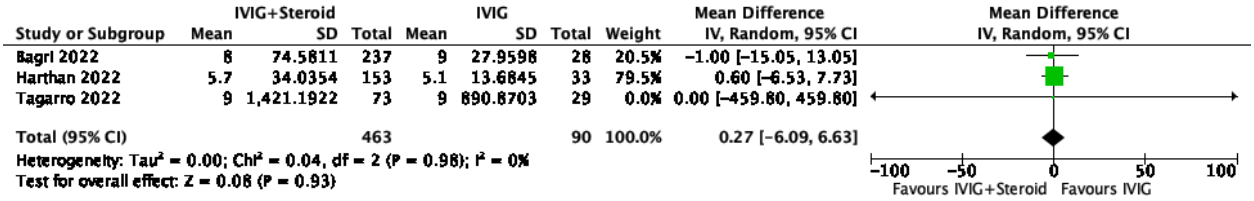


Figure 3. Comparing length of stay between IVIG + steroids vs IVIG alone

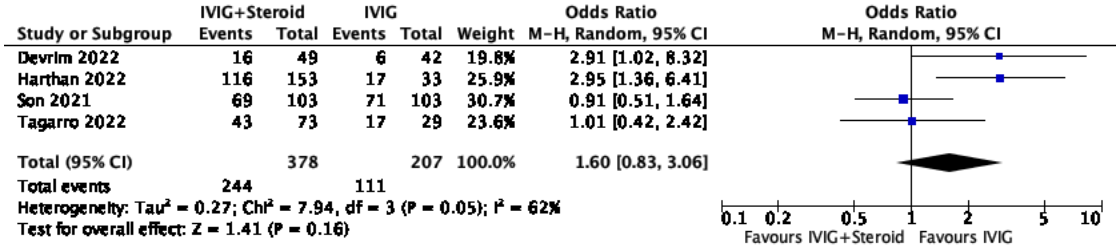


Figure 4. Comparing the need for ICU admission between IVIG + steroids vs IVIG alone

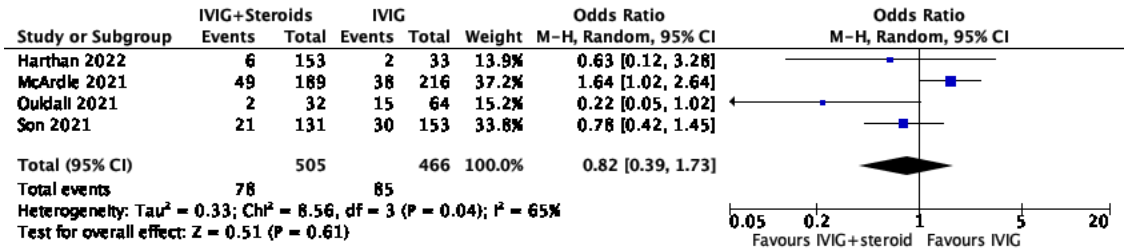


Figure 5. Comparing need for vasopressor drugs between IVIG + steroids vs IVIG alone

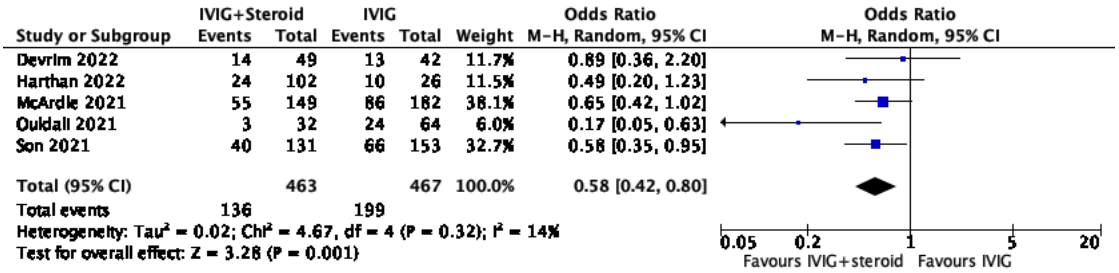


Figure 6. Comparing persistence of fever between IVIG + steroids vs IVIG alone

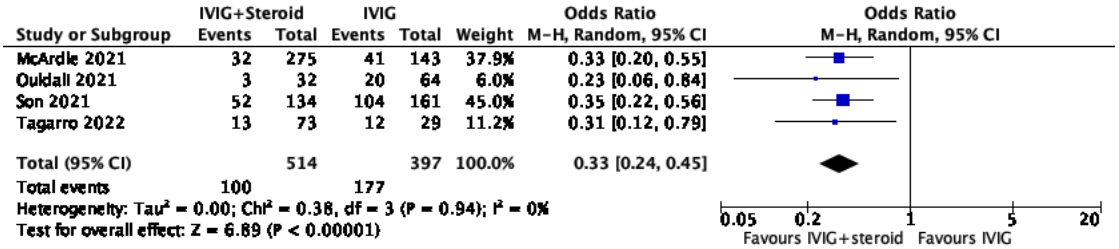


Figure 7. Comparing the need for adjunctive therapy between IVIG + steroids vs IVIG alone

Appendix 7b: Forest plots for studies comparing IVIg + Steroids versus Steroids Alone

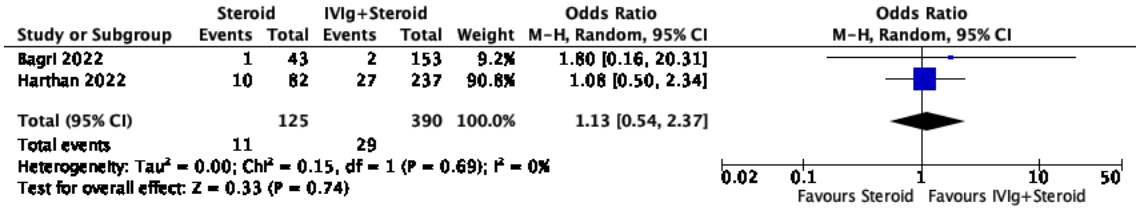


Figure 8. Comparing mortality between steroids vs IVIG + steroids

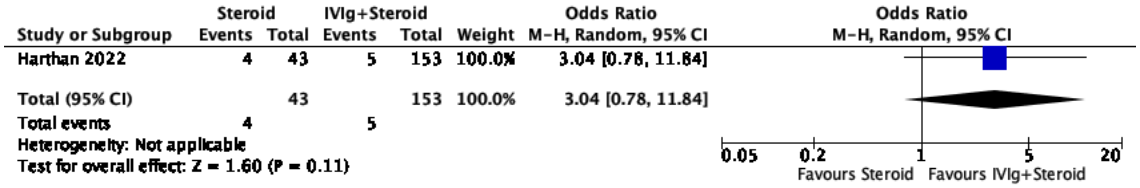


Figure 9. Comparing the need for mechanical ventilation between steroids vs IVIG + steroids

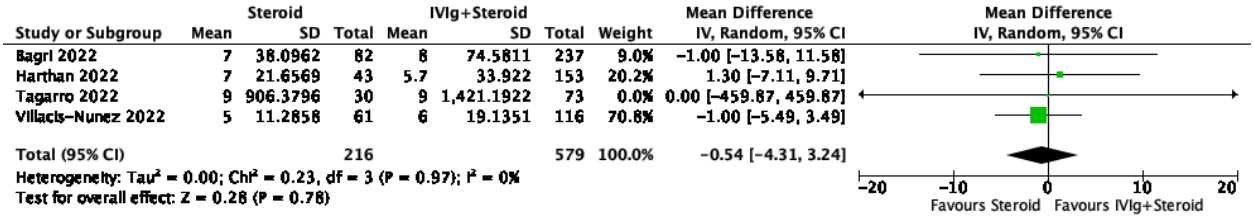


Figure 10. Comparing length of stay between steroids vs IVIG + steroids

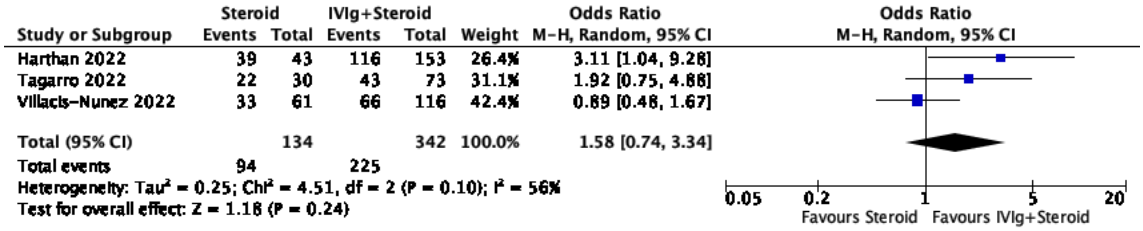


Figure 11. Comparing the need for ICU admission between steroids vs IVIG + steroids

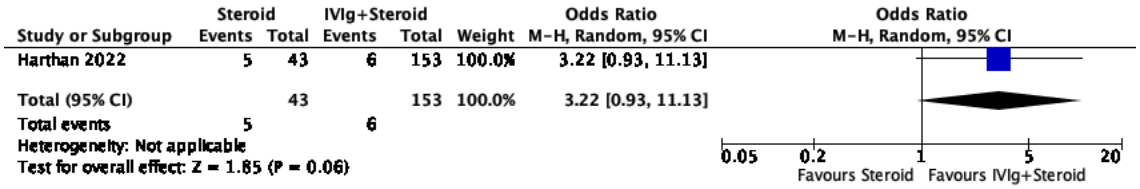


Figure 12. Comparing need for vasopressor drugs between steroids vs IVIG + steroids

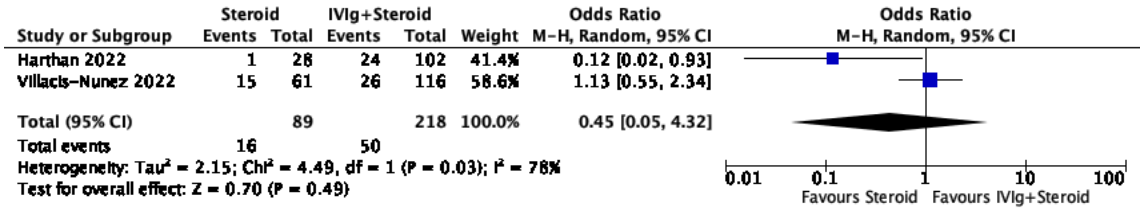


Figure 13. Comparing persistence of fever between steroid vs IVIG + steroids

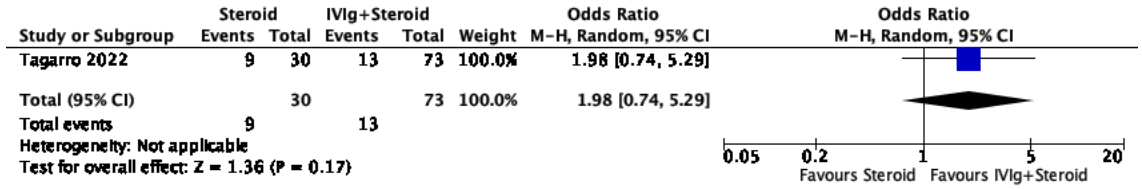


Figure 14. Comparing the need for adjunctive therapy between steroids vs IVIG + steroids

Appendix 8: Table of ongoing studies

Title	Conditions	Interventions	Characteristics	Population	Outcome measures
Multisystem Inflammatory Syndrome therapies in children (MISTIC): A randomized trial NCT04898231 Recruitment status: Recruiting Study start date: December 22, 2020 Study completion: December 23, 2023	Multisystem Inflammatory Syndrome-Children	Drug: Infliximab Anakinra Methylprednisolone	Study Type: Interventional (Clinical trial) Study Design: Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (Open Label) Primary purpose: Treatment Location: United States of America	Enrollment: 180 Age: Age <21 years old Sex: All	Primary outcome: To determine the anti-inflammatory treatment from first randomization that has the lowest rate of second randomization. Secondary outcomes: 1. To determine the anti-inflammatory treatment regimen that results in the most rapid reduction by 50 percent in the CRP level compared to baseline (pre-**IVIG**). 2. To determine the anti-inflammatory treatment regimen that results in the most rapid return to a sustained left ventricular ejection fraction of at least 55 percent from the start of the IVIG infusion. 3. To determine the anti-inflammatory treatment regimen that results in the fewest serious adverse events attributed to study drug.

Appendix 9: Local cost of drugs based on the Drug Price Reference Index [17]

Drug Name	Preparation	Drug Price Reference Index
Immunoglobulin	Normal, Human (IGIV) 50mg/mL, 100mL vial	₱15,800/vial (75^{th} percentile + 10% inflation rate)
Methylprednisolone	40mg powder for injection vial	₱716.85 (DOH COBAC Procurement Price 2021)
	125mg powder for injection + 2mL diluent vial	₱675.13/vial (Lowest + 10% inflation rate)
	500mg powder for injection vial + diluent	₱2,403.50 (75^{th} percentile + 10% inflation rate)
	1g powder for injection vial + 16mL diluent	₱3,126.50/ vial (75^{th} percentile + 10% inflation rate)
Dexamethasone	4mg/mL, 2mL solution for injection ampule	₱69.00/amp (75^{th} percentile + 10% inflation rate)
	5mg/mL, 1mL solution for injection ampule	₱67.23/amp (75^{th} percentile + 10% inflation rate)
Prednisone	10mg/5mL, 60mL oral suspension bottle	₱115.00/bottle (DOH COBAC Procurement Price 2021)
	20mg tablet	₱5.30/tab (DOH COBAC Procurement Price 2021)
	10mg tablet	₱2.70/tab (75^{th} percentile + 10% inflation rate)
	5mg tablet	₱1.42/tab (75^{th} percentile + 10% inflation rate)