South African National Department of Health
Rapid Review Report
Component: COVID-19

TITLE: INTRAVENOUS IMMUNOGLOBULIN FOR COVID-19: EVIDENCE REVIEW OF POTENTIAL BENEFIT AND HARM

Date: 6 May 2022 *(Update of initial review of 8 April 2020)*

Key findings

- An initial rapid review of available evidence was conducted in April 2020 to evaluate the efficacy and safety of intravenous immunoglobulin (IVIG) for COVID-19. However, no relevant randomised control trial (RCT) data were available then.
- An updated search was conducted in March and April 2022 and 5 RCTs pooled in a Cochrane living review (https://covid-nma.com/) was identified.
- There was no significant difference in the overall 28-day all-cause mortality rate between the IVIG and standard of care/placebo groups (RR: 1.13, 95% CI 0.80 to 1.60; 4 RCTs; n=364); very low certainty evidence.
- No difference was reported in the reduction of the risk of progression to WHO progression score level 7 or above by day 28 for IVIG compared to placebo/control: (RR 0.74; 95% CI 0.21 to 2.05; 2 RCTs, n=180), low certainty evidence.
- There was no difference in clinical improvement at day 28 among those receiving IVIG compared to the control group (RR 1.14, 95% CI 0.61 to 2.13; I^2=60.5%; 2 RCTs; n=180), very low certainty evidence.
- The number of adverse events did not differ between the IVIG group compared to the control group (RR 1.07; 95% CI 0.88 to 1.30), low certainty evidence.
- There was no difference in the number of SAEs in the IVIG arm (23/136; 16.91%) compared to the control arm (19/144; 13.19%); RR 0.93, 95% 0.27 to 3.21, low certainty evidence.
- Following the review of the evidence, it remains unclear whether IVIG reduces mortality compared to placebo or standard of care.
- Based on the number of studies available and quality of the evidence (risk of bias), there is currently insufficient evidence to support inclusion of IVIG in COVID-19 treatment guidelines in South Africa. IVIG composition is determined by the antibody profiles of the donor population and so will vary temporally and geographically, this makes extrapolating findings to the South African setting difficult. Additionally, several different doses were used for different durations.

NEML MAC ON COVID-19 THERAPEUTICS RECOMMENDATION:

	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
Type of recommendation		**X**			

Recommendation: The Committee suggests that IVIG not be used to treat COVID-19, outside of randomised trials with appropriate ethical approval.
Rationale: There is currently insufficient evidence to support inclusion of IVIG in COVID-19 treatment guidelines in South Africa.
Level of Evidence: Low certainty evidence
Review indicator: Additional high-quality evidence

(Refer to appendix 2 for the evidence to decision framework)

NEML MAC ON COVID-19 Therapeutics: Andy Parrish (chair), Gary Reubenson (vice-chair), Marc Blockman, Karen Cohen, Andy Gray, Tamara Kredo, Renee De Waal, Jeremy Nel, Helen Rees. Secretariat: Trudy Leong, Millicent Reddy.

Note: Due to the continuous emergence of new evidence, the rapid review will be updated if and when more relevant evidence becomes available.

PROSPERO registration: CRD42021286710

BACKGROUND

Intravenous immunoglobulin (IVIG) has been suggested as a possible treatment for hospitalised COVID-19 patients. Pooled from healthy donors, IVIG mainly consists of IgG with traces of IgA [1] and is indicated for several conditions, including immune thrombocytopenic purpura (ITP), Kawasaki disease and Guillain-Barré syndrome.[2,3,4]

Excessive cytokine production ('cytokine storm') as part of an hyperinflammatory response has been suggested as a cause of severe COVID-19 disease.[5,6,7] Therapeutic options aimed at ameliorating this response are being evaluated - one of these therapies is IVIG.[8]

Despite potential benefits, IVIG can also cause several adverse effects. Adverse reactions following IVIG administration include flu-like symptoms, dermatologic side effects, arrhythmias, hypotension, and transfusion-related acute lung injury (TRALI).[9] Delayed life-threatening ADRs are uncommon but include thrombotic events[10] and renal impairment.[11]

RESEARCH QUESTION: Should IVIG be used to treat hospitalised COVID-19 patients?

METHODS

This is the first update of the initial review conducted in 2020, where two electronic databases were systematically searched (Epistemonikos and www.covid-nma.com) on 4 March 2022 and 11 April 2022. The full search strategy can be found in Appendix 1. One reviewer (MR) conducted screening of records and data extraction, with results reviewed and checked by another reviewer (TL). Records were screened to identify new RCTs evaluating the effect of IVIG compared to standard of care or placebo in the management of COVID-19. The evidence (5 RCTs) from the Cochrane living review was synthesised and the study characteristics, study outcomes, risk of bias assessment and appraisal of the quality of evidence were reported in the updated rapid review. The Cochrane ROB 2.0 tool was used to appraise the risk of bias of the included RCTs and results were presented, from the Living Systematic Review on the www.covid-nma.com website. GRADE was used to assess the overall confidence of the evidence considering various factors that may decrease our confidence in the trial findings including risk of bias, inconsistency, imprecision, publication bias and indirectness. [16] The final rapid review was reviewed by a third reviewer (GR).

Eligibility criteria for review

Population: Patients hospitalised with confirmed COVID-19, no age restriction.

Intervention: Intravenous immunoglobulin either alone or in combination with another medicine. No restriction on dose, frequency, or timing with respect to onset of symptoms/severity of disease.

Comparators: Any (standard of care/placebo or active comparator).

Outcomes: Mortality, duration of hospitalisation, duration of ICU stay, duration of respiratory support, adverse reactions, clinical improvement on an ordinal scale at chosen time points

Study designs: Systematic reviews of randomized controlled trials, randomised controlled trials.

RESULTS

In February 2022, through weekly surveillance of living maps and publications we identified a systematic review and meta-analysis of 4 RCTs and 6 non-randomized trials.[12] This triggered an update of the initial IVIG review (8 April 2020). For the updated review, we searched Epistemonikos and www.covid-nma.com electronic databases on 4 March 2022 and retrieved 22 publications. A follow up search was also conducted on COVID-NMA on 11 April 2022, where 8 additional RCTs were identified. Details of each search are provided in Appendix 1. One reviewer screened the 30 records. The second reviewer confirmed these findings. The 22 studies from Epistemonikos were considered 'not relevant'. One of the 22 studies was a systematic review of 4 case series, 1 case report and 1 RCT in adults and children. This review was excluded because of the study design and the one RCT was only available in Chinese language. One study was a duplicate and the remaining 20 did not meet eligibility criteria for the review. Three RCTS on COVID-NMA investigated hyperimmune intravenous immunoglobulin and were excluded. The remaining 5 RCTs on COVID-NMA

met the inclusion criteria and are summarized here. The systematic review by Focosi et al[12] identified in February 2022, was excluded because only four of the five eligible RCTs from the covid-nma were included in this systematic review and meta-analysis publication. Therefore, in total 25 publications were excluded and 5 RCTs included. Table 1 describes the main characteristics and outcomes of 5 included RCTs. Table 2 summarises the evidence profiles. Table 3 lists the excluded studies and table 4 describes planned and ongoing registered studies.

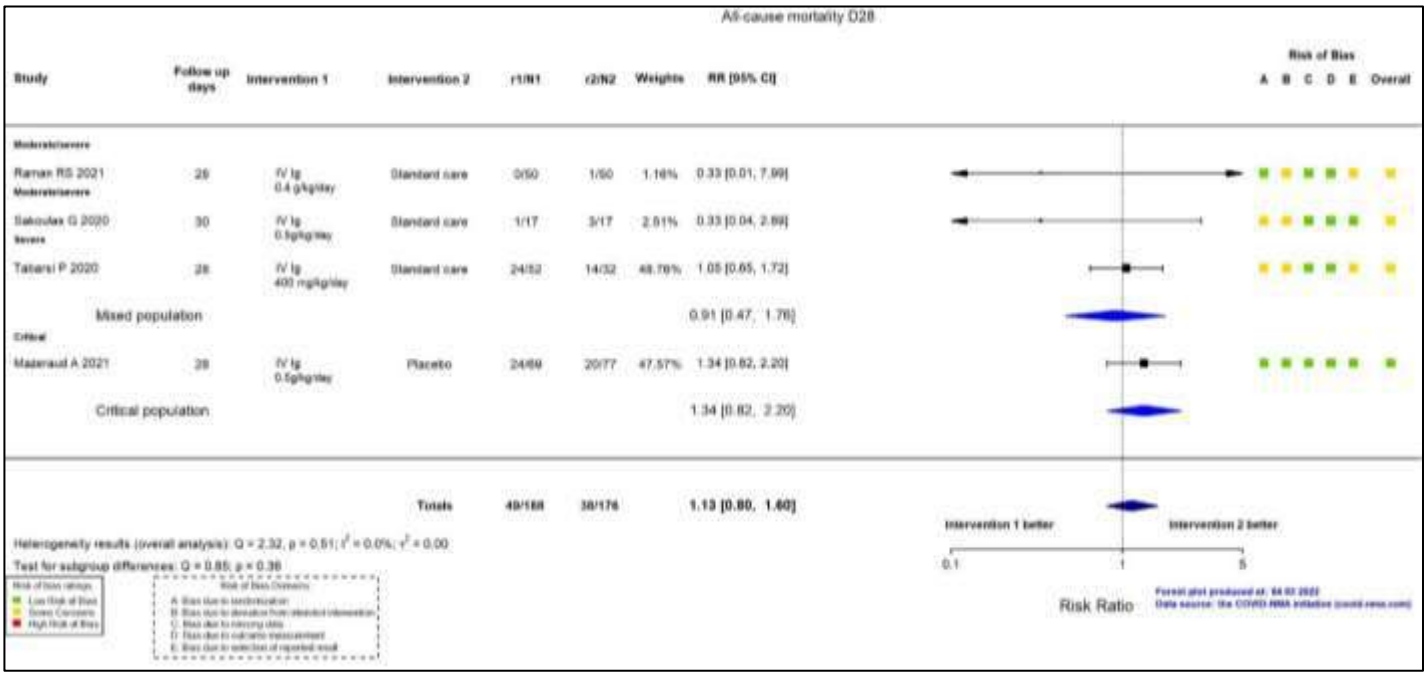
Effects of intervention(s)

The COVID-NMA living review pooled data from 5 RCTs trials (n=423)[13-17] conducted in hospitalised patients, comparing IVIG to either standard of care or placebo:

- **All-cause mortality at day 28**

There was no significant difference in the 28-day all-cause mortality rate between the IVIG and standard of care/placebo groups (RR: 1.13, 95% CI 0.80 to 1.60; 4 RCTs; n=364); very low certainty evidence - due to imprecision and some risk of bias concerns regarding randomization, deviation from intended intervention and selection of reported results.

Figure 1: Forest plot of Day 28 all-cause mortality (COVID-NMA living review)

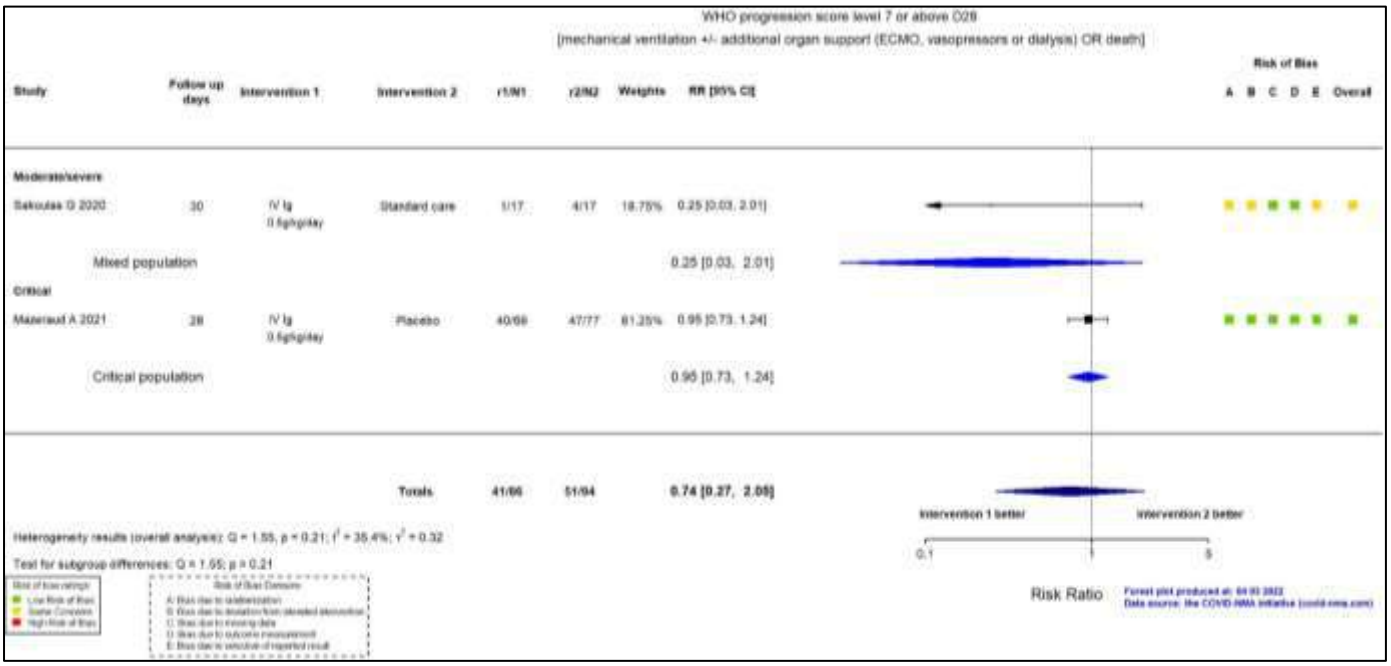


- **Clinical deterioration - mechanical ventilation +/- additional organ support (ECMO, vasopressors or dialysis) or death** [WHO progression score level 7 or above]

  No difference was reported in the reduction of the risk of progression to WHO progression score level 7 or above by day 28 for IVIG compared to placebo/control: RR 0.74; 95% CI 0.21 to 2.05; 2 RCTs, n=180, see figure 2. Evidence was assessed as low certainty evidence due to very serious imprecision.

  Note that individual outcomes of duration of hospitalisation, duration of ICU stay or duration of respiratory support was not reported separately in the COVID-NMA living review.

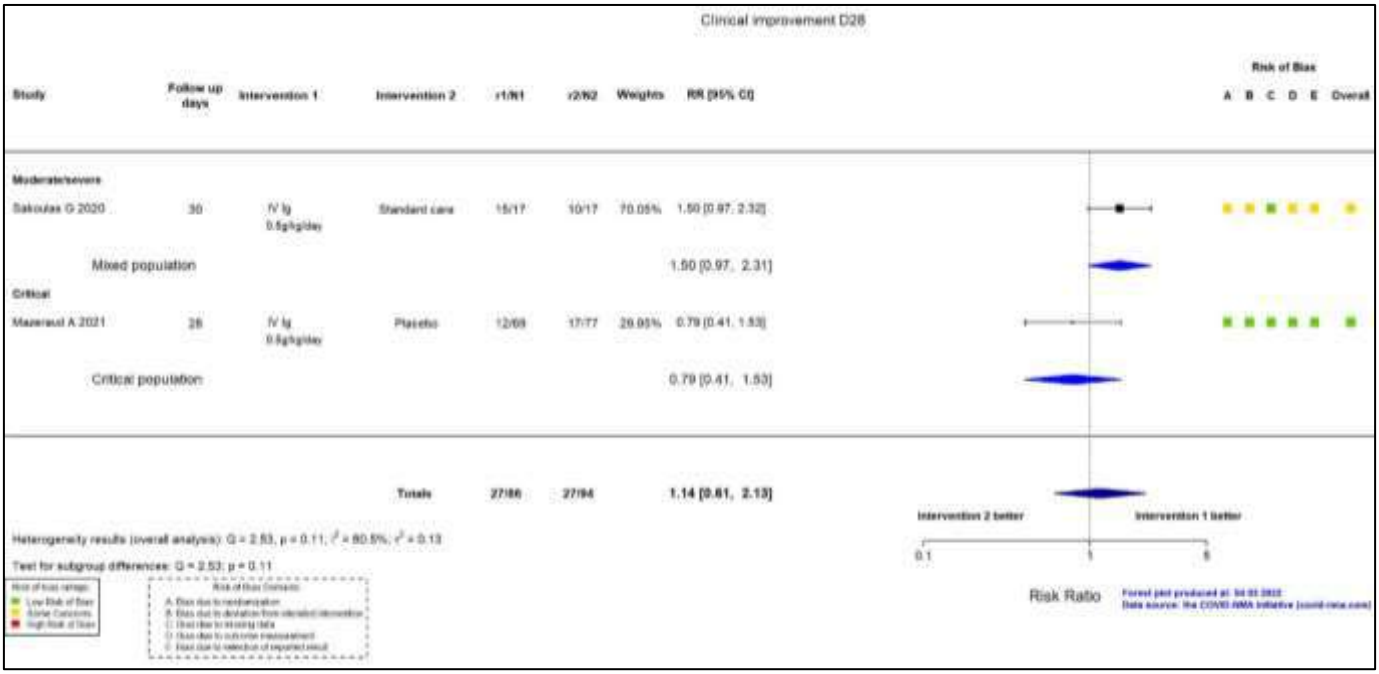
Figure 2: Forest plot of WHO progression score level 7 or above at day 28 Day 28 (COVID-nma living review)



- **Clinical improvement at day 28**

  There was no difference in clinical improvement at day 28 among those receiving IVIG compared to the control group (RR 1.14, 95% CI 0.61 to 2.13; I^2=60.5%; 2 RCTs; n=180), very low certainty evidence with high imprecision, inconsistency and serious risk of bias.

Figure 3: Forest plot of clinical improvement at day 28 (COVID-NMA living review)



- **Adverse events**

  The number of adverse events did not differ between the IVIG group compared to the control group (RR 1.07; 95% CI 0.88 to 1.30). This was assessed as low certainty evidence for concerns of imprecision due to the low number of study participants (n=246, 3 RCTs).

- **Serious adverse events (SAEs)**

  There was no difference in the number of SAEs in the IVIG arm (23/136; 16.91%) compared to the control arm (19/144; 13.19%); RR 0.93, 95% 0.27 to 3.21, assessed as low certainty due to very serious imprecision and low number of study participants (n=280, 3 RCTs).

CONCLUSION

It is unclear whether IVIG reduces mortality, improves the risk of clinical deterioration or results in clinical improvement amongst hospitalised COVID-19 patients, compared to placebo or standard of care. IVIG composition is determined by the antibody profiles of the donor population and so will vary temporally and geographically, this makes extrapolating findings to the South African setting difficult. Additionally, several different doses were used for different durations. Currently, there is insufficient evidence to support inclusion of IVIG in COVID-19 treatment guidelines in South Africa.

Reviewers:

Trudy Leong, Milli Reddy, Gary Reubenson

Declaration of interests: TL (National Department of Health, Essential Drugs Programme, South Africa), MR (Better Health Program, South Africa), GR (Rahima Moosa Mother & Child Hospital, Johannesburg) have no applicable interests to declare in respect of IVIG therapy for COVID-19.

Table 1. Characteristics of included studies

Citation	Study design	Population (n)	Treatment	Main findings	Risk of bias assessment
Mazeraud A, et al. Intravenous immunoglobulins in patients with COVID-19-associated moderate-to-severe acute respiratory distress syndrome (ICAR): multicentre, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med. 2022 Feb;10(2):158-166. doi: 10.1016/S2213-2600(21)00440-9. Error! Bookmark not defined. NCT04350580; EudraCT2020-001570-30	RCT: Double blinding	n= 146 • IVIG=69 • Placebo=77 • 103 males • Severity: Critical - n=146 Multicenter: France (n=27) Follow-up duration (days): 90	IVIG (Four intravenous perfusions of 0.5g/kg each given over at least 8 h over 4 days) *vs* Placebo	IVIG group vs placebo **Intention-to-treat analysis** **Median number of ventilation-free days at day 28:** (0·0 [IQR 0·0–8·0]) vs (0·0 [0·0–6·0]; difference estimate 0·0 [0·0–0·0]; p=0·21). **Serious adverse events:** 78 events in 22 [32%] patients vs 47 events in 15 [20%] patients; p=.·089.	Overall risk of bias: **LOW RISK** • Randomisation: **LOW RISK** • Deviations from intervention: **LOW RISK** • Missing outcome data: **LOW RISK** • Measurement of the outcome: **LOW RISK** • Selection of the reported results: **LOW RISK**
Raman RS, et al. A Phase II Safety and Efficacy Study on Prognosis of Moderate Pneumonia in Coronavirus Disease 2019 Patients With Regular Intravenous Immunoglobulin Therapy. J Infect Dis. 2021 May 20;223(9):1538-1543. doi: 10.1093/infdis/jiab098. Error! Bookmark not defined. CTRI/2020/06/026222	RCT: Unblinded	n= 100 • IVIG=50 • Standard care=50 • 33 males Multicenter: India (n=7) Follow-up duration (days): 28	IVIG (0.4 g/kg body weight IV once daily for 5 days) PLUS Standard of Care (SOC) *vs* SOC alone	IVIG group vs SOC **Number of days from initiation of treatment to hospital discharge:** 7.7 vs. 17.5 days; p=0.0001.	Overall risk of bias: **MODERATE RISK** • Randomisation: **LOW RISK** • Deviations from intervention: **MODERATE RISK** • Missing outcome data: **LOW RISK** • Measurement of the outcome: **MODERATE RISK** • Selection of the reported results: **MODERATE RISK**
Tabarsi P, et al. Evaluating the effects of Intravenous Immunoglobulin (IVIg) on the management of severe COVID-19 cases: A randomized controlled trial. Int Immunopharmacol. 2021 Jan;90:107205. doi: 10.1016/j.intimp.2020.107205. Error! Bookmark not defined. IRCT20151227025726N20.	RCT: Unblinded	n= 84 • IVIG=52 • Standard care=32 • 65 males • Severity: Severe: n=84 Single center: Iran Follow-up duration (days): 28	IVIG (400 mg/kg IV once a day for 3 days) *vs* Control	IVIG group vs placebo **Need for invasive mechanical ventilation and oxygenation:** 21/52 vs 10/32; P= 0.3 **Need for admission to the Intensive Care Unit (ICU):** 39/52 vs 27/32; p= 0.3 **Mortality rate:** 24/52 vs 14/32; p= 0.8	Overall risk of bias: **MODERATE RISK** • Randomisation: **MODERATE RISK** • Deviations from intervention: **MODERATE RISK** • Missing outcome data: **LOW RISK** • Measurement of the outcome: **LOW RISK** • Selection of the reported results: **MODERATE RISK**
Gharebaghi N, et al. The use of intravenous immunoglobulin gamma for the treatment of severe coronavirus disease 2019: a randomized placebo-controlled double-blind clinical trial. BMC Infect Dis. 2020 Oct 21;20(1):786. doi: 10.1186/s12879-020-05507-4. Erratum in: BMC Infect Dis. 2020 Nov 26;20(1):895. Error! Bookmark not defined. IRCT20200501047259N1	RCT: double blinding	n= 59 • IVIG=30 • Placebo=29 • Mean age: NR • 41 males Single center: Iran	IVIG (5 g IV four times a day for 3 consecutive days) *vs* Placebo	IVIG group vs placebo **In hospital mortality:** (6/30 [20.0%] vs. 14/29 [48.3%], respectively; P = 0.022). **Multivariate regression analysis** **Administration of IVIG on mortality rate:** (aOR = 0.003 [95% CI: 0.001–0.815]; p= 0.042).	Overall risk of bias: **LOW RISK** • Randomisation: **LOW RISK** • Deviations from intervention: **LOW RISK** • Missing outcome data: **LOW RISK** • Measurement of the outcome: **LOW RISK** • Selection of the reported results: **LOW RISK**
Sakoulas G, et al. Intravenous Immunoglobulin Plus Methylprednisolone Mitigate Respiratory Morbidity in Coronavirus Disease 2019. Crit Care Explor. 2020 Nov 16;2(11):e0280. doi: 10.1097/CCE.0000000000000280.. Error! Bookmark not defined. CTRI/2020/06/026222	RCT: Unblinded	n= 34 • IVIG=17 • SOC=17 • 20 males • Severity: Moderate: n=7; Severe: n=26 Location: Multicenter / USA (n=2) Follow-up duration (days): 30	IVIG (0.5 g/kg IV once a day for 3 days) *vs* SOC	IVIG group vs SOC **Progression to requiring mechanical ventilation:** (2/14 vs 7/12, p = 0.038) **Median hospital length of stay:** (11 vs 19 days, p = 0.01) **Median ICU stay:** (2.5 vs 12.5 d, p = 0.006 **Improvement in Pao2/Fio2 at 7 days:** (median [range] change from time of enrollment +131 [+35 to+330] vs +44·5 [–115 to +157], p = 0.01	Overall risk of bias: **MODERATE RISK** • Randomisation: **MODERATE RISK** • Deviations from intervention: **MODERATE RISK** • Missing outcome data: **LOW RISK** • Measurement of the outcome: **MODERATE RISK** • Selection of the reported results: **MODERATE RISK**

Citation	Study design	Population (n)	Treatment	Main findings	Risk of bias assessment
				Pao2/Fio2 improvement at day 7: was significantly < for the SOC patients who received glucocorticoid therapy than those in the IV immunoglobulin arm (p = 0.0057)	

Table 2: Summary of findings

Question: IVIG compared to standard care/placebo for the treatment of COVID-19

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IVIG	SOC/ placebo	Relative (95% CI)	Absolute (95% CI)	
All-cause mortality (follow-up: 28 days)											
4	RCTs	serious[a]	not serious [a]	not serious	very serious[b]	none	49/188	38/176	**RR 1.13** (0.80 to 1.60)	**28 more per 1,000** (from 43 fewer to 130 more)	⊕◯◯◯ Very low
Clinical deterioration - mechanical ventilation +/- additional organ support (ECMO, vasopressors or dialysis) or death [WHO progression score level 7 or above]											
2	RCTs	not serious	not serious	not serious	very serious[b]	none	41/86	51/94	**RR 0.74** (0.27 to 2.05)	**22 fewer per 1000** (from 38 fewer to 5 fewer)	⊕⊕◯◯ Low
Clinical improvement (follow-up: 28 days)											
2	RCTs	serious[a]	serious[c]	not serious	very serious[b]	none	27/86	27/94	**RR 1.14** (0.61 to 2.13)	**40 more per 1000** (from 112 fewer to 325 more)	⊕◯◯◯ Very low
Adverse events											
3	RCTs	not serious	not serious	not serious	very serious[b]	none	66/119	66/127	**RR 1.07** (0.88 to 1.30)	**36 more per 1,000** (from 62 fewer to 156 more)	⊕⊕◯◯ Low
Serious adverse events											
3	RCTs	not serious	not serious	not serious	very serious[b]	none	135/812	170/811	**RR 0.93** (0.27 to 3.21)	**9 fewer per 1,000** (from 96 fewer to 292 more)	⊕⊕◯◯ Low

CI: confidence interval; **RCT:** randomised control trial; **RR:** risk ratio

Explanations

a. Risk of bias downgraded by 1 level: some concerns regarding adequate randomization, deviation from intended intervention and selection of reported results

b. Due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of participants and events

c. Inconsistency downgraded by 1 level: I^2=:60.5%.

Table 3. List of Excluded Studies

#	Citation	Reason for exclusion
1.	Abu-Rumeileh, S., et al. (2020). "Guillain-Barré syndrome spectrum associated with COVID-19: an up-to-date systematic review of 73 cases." Journal of neurology.	Did not meet PICO criteria
2.	Artemiadis, A., et al. (2021). "Myelopathy associated with SARS-COV-2 infection. A systematic review." Neurological research: 1-9.	Did not meet PICO criteria
3.	Bastug, A., et al. (2021). "Multiple system inflammatory syndrome associated with SARS-CoV-2 infection in an adult and an adolescent." Rheumatology international.	Did not meet PICO criteria
4.	Ghosh, R., et al. (2021). "De Novo Movement Disorders and COVID-19: Exploring the Interface." Mov. Disord. Clin. Pract.	Did not meet PICO criteria
5.	Goudarzi, S., et al. (2021). "Treatment Options for COVID-19-Related Guillain-Barré Syndrome: A Systematic Review of Literature." The neurologist 26(5): 196-224.	Did not meet PICO criteria
6.	Jingyi, Z., et al. (2020). "Effectiveness of Intravenous Immunoglobulin for Children with Severe COVID-19: A Rapid Review." medRxiv.	Did not meet PICO criteria – systematic review of 4 case series and 1 case report. The one RCT included was only available in Chinese language
7.	Kamel, W. A., et al. (2021). "Guillain-Barre Syndrome following COVID-19 Infection: First Case Report from Kuwait and Review of the Literature." Dubai Med. J.	Did not meet PICO criteria
8.	Llinas-Caballero, K., et al. (2021). "Kawasaki disease in Colombia: A systematic review and contrast with multisystem inflammatory syndrome in children associated with COVID-19." Rev. Colomb. Reumatol.	Did not meet PICO criteria
9.	Mahapure, K. S., et al. (2021). "COVID-19-Associated Acute Disseminated Encephalomyelitis: A Systematic Review." Asian journal of neurosurgery 16(3): 457-469.	Did not meet PICO criteria
10.	Maria, S., et al. (2021). "Neurological, neuropsychiatric and psychiatric symptoms during COVID-19 infection and after recovery: a systematic review of observational studies." medRxiv.	Did not meet PICO criteria
11.	Martins, M. M., et al. (2021). "Update on SARS-CoV-2 infection in children." Paediatrics and international child health: 1-9.	Did not meet PICO criteria
12.	Novikova, Y. Y., et al. (2020). "Clinical, laboratory-instrumental characteristics, course and therapy of pediatric multisystem inflammatory syndrome associated with covid-19." Pediatriya 99(6): 73-83.	Did not meet PICO criteria
13.	Oltean, M., et al. (2020). "Covid-19 in kidney transplant recipients: a systematic review of the case series available three months into the pandemic." Infectious diseases (London, England) 52(11): 1-8.	Did not meet PICO criteria
14.	Radia, T., et al. (2021). "Multi-system inflammatory syndrome in children & adolescents (MIS-C): A systematic review of clinical features and presentation." Paediatric respiratory reviews 38: 51-57.	Did not meet PICO criteria
15.	Roveron, D. L., et al. (2021). "Myasthenia gravis and COVID-19: a systematic review of case reports and case series." Rev. patol. trop 50(2): 1-20.	Did not meet PICO criteria
16.	Shioji, N., et al. (2021). "Multisystem inflammatory syndrome in children during the coronavirus disease pandemic of 2019: a review of clinical features and acute phase management." Journal of anesthesia.	Did not meet PICO criteria
17.	Siahaan, Y., et al. (2020). "COVID-19-Associated Encephalitis: Systematic Review of Case Reports Findings on Cytokine-Immune-Mediated Inflammation as an Underlying Mechanism." ResearchSquare.	Did not meet PICO criteria
18.	Tang, Y., et al. (2021). "Multisystem inflammatory syndrome in children during the coronavirus disease 2019 (COVID-19) pandemic: a systematic review of published case studies." Translational pediatrics 10(1): 121-135.	Did not meet PICO criteria
19.	Uncini, A., et al. (2020). "Guillain-Barré syndrome in SARS-CoV-2 infection: an instant systematic review of the first six months of pandemic." Journal of neurology, neurosurgery, and psychiatry 91(10): 1105-1110.	Did not meet PICO criteria
20.	Williams, V., et al. (2022). "Clinicolaboratory Profile, Treatment, Intensive Care Needs, and Outcome of Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2: A Systematic Review and Meta-analysis." J. Pediatr. Intensive Care 11(1): 1-12.	Did not meet PICO criteria
21.	Zhang, Q. Y., et al. (2021). "Similarities and differences between multiple inflammatory syndrome in children associated with COVID-19 and Kawasaki disease: clinical presentations, diagnosis, and treatment." World journal of pediatrics : WJP.	Did not meet PICO criteria
22	ITAC (INSIGHT 013) Study Group. Hyperimmune immunoglobulin for hospitalised patients with COVID-19 (ITAC): a double-blind, placebo-controlled, phase 3, randomised trial. Lancet. 2022 Feb 5;399(10324):530-540. doi: 10.1016/S0140-6736(22)00101-5.	Did not meet PICO criteria
23	Devang Parikh, et al. (2021). Safety and Efficacy of COVID-19 Hyperimmune Globulin (HIG) Solution in the Treatment of Active COVID-19 infection- Findings from a Prospective, Randomized, Controlled, Multi-Centric Trial. The Indian Practitioner, 74(11), 15-22.	Did not meet PICO criteria – included hyperimmune immunoglobulin
24	Ali S, et al. Hyperimmune anti-COVID-19 IVIG (C-IVIG) treatment in severe and critical COVID-19 patients: A phase I/II randomized control trial. EClinicalMedicine. 2021 Jun;36:100926. doi: 10.1016/j.eclinm.2021.100926.	Did not meet PICO criteria – included hyperimmune immunoglobulin
25	Focosi D, et al Efficacy of High-Dose Polyclonal Intravenous Immunoglobulin in COVID-19: A Systematic Review. Vaccines (Basel). 2022 Jan 9;10(1):94. doi: 10.3390/vaccines10010094.	Did not meet PICO criteria

Table 4. Characteristics of planned and ongoing clinical trials – (updated search of 2 May 2022)

Treatment (per arm)	Sample size	Severity at enrollment	Sponsor/Funder	Reg. number	Full text link;
(1) Human immunoglobulin vs (2) Placebo	50	Moderate	Regents of the University of Minnesota	EUCTR2020-002542-16-DK	https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-002542-16/DK
(1) Anakinra vs (2) Aspirin vs (3) Azithromycin vs (4) Baricitinib vs (5) Colchicine vs (6) Convalescent plasma vs (7) Corticosteroid vs (8) Dimethyl fumarate vs (9) Empagliflozin vs (10) Corticosteroid vs (11) Hydroxychloroquine vs (12) Immunoglobulin vs (13) Lopinavir + ritonavir vs (14) Molnupiravir vs (15) Nirmatrelvir + ritonavir vs (16) Sotrovimab vs (17) Standard of care vs (18) Synthetic neutralising antibodies vs (19) Tocilizumab	50000	Moderate/severe/critical	University of Oxford	NCT04381936	https://clinicaltrials.gov/show/NCT04381936
(1) Methylprednisolone vs (2) Human immunoglobulin	120	No restriction on type of patients	University Children's Hospital Basel	NCT04826588	https://clinicaltrials.gov/show/NCT04826588
(1) Human immunoglobulin vs (2) Placebo	1084	Mild	Adagio Pharmaceuticals Inc	CTRI/2021/12/038474	http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=62557
(1) Immunoglobulin vs (2) Standard of care	80	Severe	Peking Union Medical College Hospital	NCT04261426	https://clinicaltrials.gov/show/NCT04261426
(1) Immunoglobulin vs (2) Placebo	208	Severe	Octapharma	NCT04400058	https://clinicaltrials.gov/show/NCT04400058
(1) Human immunoglobulin vs (2) Standard of care	60	Severe	Lok Nayak Hospital	CTRI/2021/05/033622	http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=56002
(1) Immunoglobulin vs (2) Standard of care	100	Moderate/severe	Virchow Biotech Private Limited	CTRI/2020/06/026222	http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=44299
(1) Immunoglobulin vs (2) Standard of care	310	Severe	Dow University of Health Sciences	NCT04891172	https://clinicaltrials.gov/show/NCT04891172
(1) Immunoglobulin vs (2) Placebo	146	Critical	Centre Hospitalier St Anne	NCT04350580	https://clinicaltrials.gov/show/NCT04350580
(1) Convalescent plasma vs (2) Human immunoglobulin	196	Severe	Centenario Hospital Miguel Hidalgo	NCT04381858	https://clinicaltrials.gov/show/NCT04381858
(1) Immunoglobulin vs (2) Standard of care	100	Moderate	Instituto Grifols, S.A.	NCT04432324,	https://clinicaltrials.gov/show/NCT04432324
(1) Immunoglobulin vs (2) Standard of care	100	Severe	Grifols Therapeutics LLC	NCT04480424	https://clinicaltrials.gov/show/NCT04480424
(1) Immunoglobulin vs (2) Standard of care	34	Moderate/severe	George Sakoulas, MD	NCT04411667	https://clinicaltrials.gov/show/NCT04411667
(1) Immunoglobulin vs (2) Standard of care	76	Moderate/severe	Biopharma Plasma LLC	NCT04500067	https://clinicaltrials.gov/show/NCT04500067
(1) Immunoglobulin vs (2) Standard of care	60	Moderate/severe	University of Health Sciences Lahore	NCT04548557	https://clinicaltrials.gov/show/NCT04548557
(1) Hydroxychloroquine + lopinavir + ritonavir vs (2) Hydroxychloroquine + immunoglobulin + lopinavir + ritonavir	80	Severe	Shahid Beheshti University of Medical Sciences	IRCT20151227025726N20	http://en.irct.ir/trial/49638
(1) Immunoglobulin vs (2) Standard of care	100	Severe	Tabriz University of Medical Sciences	IRCT20200317046797N3	http://en.irct.ir/trial/47014
(1) Convalescent plasma vs (2) Immunoglobulin vs (3) Standard of care	15	Severe/critical	Birjand University of Medical Sciences	IRCT20200413047056N1	http://en.irct.ir/trial/47212
(1) Immunoglobulin vs (2) Placebo	40	Severe	Oroumia University of Medical Sciences	IRCT20200501047259N1	http://en.irct.ir/trial/47609

Appendix 1: Search strategy

PubMed

(("immunoglobulins"[MeSH Terms] OR "immunoglobulins"[All Fields] OR "immunoglobulin"[All Fields]) AND ("COVID-19"[All Fields] OR "COVID-2019"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "2019-nCoV"[All Fields] OR "SARS-CoV-2"[All Fields] OR "2019nCoV"[All Fields] OR (("Wuhan"[All Fields] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields])) AND (2019/12[PDAT] OR 2020[PDAT])))) AND "humans"[MeSH Terms]

Output 22 records, all excluded as not relevant to PICO question

Epistemonikos

(title:((title:(intravenous immunoglobulin) OR abstract:(intravenous immunoglobulin)) AND (title:(respiratory) OR abstract:(respiratory))) OR abstract:((title:(intravenous immunoglobulin) OR abstract:(intravenous immunoglobulin)) AND (title:(respiratory) OR abstract:(respiratory))))

Output 22 records, all excluded as not relevant to PICO question **(1 Duplicate)**

www.covid-nma.com

Intravenous immunoglobulin

Output 8 records (3 Excluded and 5 relevant)

Appendix 2: Evidence to decision framework

Desirable Effects		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ **Don't know**	Refer to Table 2: Summary of findings. *IVIG vs placebo/ standard of care:* • **All-cause mortality (follow-up D28):** RR 1.13 (0.80 to 1.60) • **Clinical deterioration - mechanical ventilation +/- additional organ support (ECMO, vasopressors or dialysis) or death [WHO progression score level 7 or above]:** RR 0.74 (0.27 to 2.05) • **Clinical improvement (follow-up D28):** RR 1.14 (0.61 to 2.13)	

Undesirable Effects		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large ○ Moderate ○ **Small** ○ Trivial ○ Varies ○ Don't know	Refer to Table 2: Summary of findings. *IVIG vs placebo/ standard of care:* • **Adverse events:** RR 1.07 (0.88 to 1.30) • **Serious adverse events**: RR 0.93 (0.27 to 3.21)	

Certainty of evidence: What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ **Very low** ○ Low ○ Moderate ○ High ○ No included studies	Refer to Table 2: Summary of findings	Very low quality of evidence due to serious imprecision, inconsistency and serious risk of bias

Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ **Important uncertainty or variability** ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability		There is a lack of research evidence from stakeholders.

Balance of effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ **Does not favor either the intervention or the comparison** ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		Available evidence does not provide compelling evidence of benefit for IVIG in hospitalized COVID-19 patients.

Resources required: How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Large costs ○ **Moderate costs** ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	No specific resource-use evaluation performed, as available evidence does not provide compelling evidence of benefit for IVIG in hospitalized COVID-19 patients.	

Cost effectiveness: Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ **Probably favors the comparison** ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	No specific resource-use evaluation performed, as available evidence does not provide compelling evidence of benefit for IVIG in hospitalized COVID-19 patients.	Illustrative cost example: R5490.85 for 12g vial, so based on 60kg adult at 0.4/kg/d x 5d = R54908.50 per patient - excluding other consumables Contract circular HP10-2021BIO (April 2022)

Equity: What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ **Probably reduced** ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		IVIG is often in short supply, so use in COVID-19 patients may reduce availability for use in patients with other conditions treated with IVIG e.g. ITP, GBS, MIS-C, Kawasaki disease, Primary immune deficiencies

Acceptability: Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ **Probably yes** ○ Yes ○ Varies ○ Don't know	There is a lack of research evidence from stakeholders	IVIG already used by clinicians for other indications so likely to be considered acceptable to prescribers and patients.

Feasibility: Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ **Probably no** ○ Probably yes ○ Yes ○ Varies ○ Don't know		Supply constraints likely during a severe wave (though would not be rational use of IVIG).

Version control:

Version	Date	Reviewer(s)	Recommendation and Rationale
1	8 April 2020	TL, JR, GR	There is currently insufficient evidence to support inclusion of IVIG in treatment guidelines for COVID-19 in South Africa until further data become available. Eligible patients with COVID-19 in South Africa should be considered for enrolment in relevant therapeutic trials.
2	4 May 2022	TL, MR, GR	IVIG should not be used to treat COVID-19, outside of randomised trials with appropriate ethical approval as there is currently insufficient evidence to support inclusion of IVIG in COVID-19 treatment guidelines in South Africa.

For internal NDoH use:
WHO INN: immunoglobulins, normal human, for intravascular adm.
ATC: J06BA02
ICD10: U07.1/U07.2

References

[1] Barahona Afonso AF, João CM. The Production Processes and Biological Effects of Intravenous Immunoglobulin. Biomolecules. 2016 Mar 9;6(1):15. https://www.ncbi.nlm.nih.gov/pubmed/27005671

[2] Qin YH, Zhou TB, Su LN, Lei FY, Zhao YJ, Huang WF. The efficacy of different dose intravenous immunoglobulin in treating acute idiopathic thrombocytopenic purpura: a meta-analysis of 13 randomized controlled trials. Blood Coagul Fibrinolysis. 2010 Dec;21(8):713-21. https://www.ncbi.nlm.nih.gov/pubmed/2096262

13. Li T. The Efficacy of Intravenous Immunoglobulin Therapy for Severe 2019-nCoV Infected Pneumonia. Clinicaltrialsgov. 2020. https://clinicaltrials.gov/ct2/show/NCT0426142

[3] Chen S, Dong Y, Yin Y, Krucoff MW. Intravenous immunoglobulin plus corticosteroid to prevent coronary artery abnormalities in Kawasaki disease: a meta-analysis. Heart. 2013 Jan;99(2):76-82. https://www.ncbi.nlm.nih.gov/pubmed/2286967

[4] Hughes RA, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-Barré syndrome. Cochrane Database Syst Rev. 2014 Sep 19;(9):CD002063. https://www.ncbi.nlm.nih.gov/pubmed/25238327

[5] Yang, Y. et al. Exuberant elevation of IP-10, MCP-3 and IL-1ra during SARS-CoV-2 infection is associated with disease severity and fatal outcome. Preprint at medRxiv https://doi.org/10.1101/2020.03.02.20029975(2020)

[6] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020 Mar 28;395(10229):1033-1034. https://www.ncbi.nlm.nih.gov/pubmed/3219257

[7] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497–506.

[8] Guo Y, Tian X, Wang X, Xiao Z. Adverse Effects of Immunoglobulin Therapy. Front Immunol. 2018 Jun 8;9:1299. https://www.ncbi.nlm.nih.gov/pubmed/2995105

[9] Woodruff RK, Grigg AP, Firkin FC, Smith IL. Fatal thrombotic events during treatment of autoimmune thrombocytopenia with intravenous immunoglobulin in elderly patients. Lancet. 1986 Jul 26;2(8500):217-8. https://www.ncbi.nlm.nih.gov/pubmed/287345

[10] Woodruff RK, Grigg AP, Firkin FC, Smith IL. Fatal thrombotic events during treatment of autoimmune thrombocytopenia with intravenous immunoglobulin in elderly patients. Lancet. 1986 Jul 26;2(8500):217-8. https://www.ncbi.nlm.nih.gov/pubmed/2873457

[11] Rault R, Piraino B, Johnston JR, Oral A. Pulmonary and renal toxicity of intravenous immunoglobulin. Clin Nephrol. 1991 Aug;36(2):83-6. https://www.ncbi.nlm.nih.gov/pubmed/193466

[12] Focosi D, et al Efficacy of High-Dose Polyclonal Intravenous Immunoglobulin in COVID-19: A Systematic Review. Vaccines (Basel). 2022 Jan 9;10(1):94. doi: 10.3390/vaccines10010094

13. Mazeraud A, Jamme M, Mancusi RL, Latroche C, Megarbane B, Siami S, et al. Intravenous immunoglobulins in patients with COVID-19-associated moderate-to-severe acute respiratory distress syndrome (ICAR): multicentre, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med. 2022 Feb;10(2):158-166. doi: 10.1016/S2213-2600(21)00440-9.

14. Raman RS, Bhagwan Barge V, Anil Kumar D, Dandu H, Rakesh Kartha R, et al. A Phase II Safety and Efficacy Study on Prognosis of Moderate Pneumonia in Coronavirus Disease 2019 Patients With Regular Intravenous Immunoglobulin Therapy. J Infect Dis. 2021 May 20;223(9):1538-1543. doi: 10.1093/infdis/jiab098.

15. Tabarsi P, Barati S, Jamaati H, Haseli S, Marjani M, Moniri A, et al. Evaluating the effects of Intravenous Immunoglobulin (IVIg) on the management of severe COVID-19 cases: A randomized controlled trial. Int Immunopharmacol. 2021 Jan;90:107205. doi: 10.1016/j.intimp.2020.107205.

16. Gharebaghi N, Nejadrahim R, Mousavi SJ, Sadat-Ebrahimi SR, Hajizadeh R. The use of intravenous immunoglobulin gamma for the treatment of severe coronavirus disease 2019: a randomized placebo-controlled double-blind clinical trial. BMC Infect Dis. 2020 Oct 21;20(1):786. doi: 10.1186/s12879-020-05507-4. Erratum in: BMC Infect Dis. 2020 Nov 26;20(1):895.

17. Sakoulas G, Geriak M, Kullar R, Greenwood KL, Habib M, Vyas A, et al. Intravenous Immunoglobulin Plus Methylprednisolone Mitigate Respiratory Morbidity in Coronavirus Disease 2019. Crit Care Explor. 2020 Nov 16;2(11):e0280. doi: 10.1097/CCE.0000000000000280.

18. Living mapping and living network meta-analysis of COVID-19 studies: Intravenous immunoglobulin vs standard of care/ placebo. https://covid-nma.com/living_data/index.php?comparison=35