Rapid Evidence Review

Clinical evidence for the use of intravenous immunoglobulin in the treatment of COVID-19

Version 2, 14th May 2020

National Centre for Pharmacoeconomics
NCPE Ireland

Medicines Management Programme

Prepared by the COVID-19 Evidence Review Group with clinical contribution from Dr. Niall Conlon, Consultant Immunologist, St. James Hospital, Dr. Mary Keogan, Clinical Lead National Clinical Programme for Pathology & Consultant Immunologist, Beaumont Hospital.

Key changes between version 1 and version 2 (14th May 2020)

A number of case reports describing the use of IVIG are included in this version and 2 additional studies which focused specifically on the use of IVIG in patients with COVID-19 – one case series and one retrospective cohort study (available as a pre-print). A number of guidelines have included a reference to IVIG, but the general consensus is not to use IVIG. The recent reports of Kawasaki Disease in children with COVID-19 highlight the role of IVIG and aspirin to treat this condition and supporting evidence of its benefit are available from 2 case reports and one case series.

The COVID-19 Evidence Review Group for Medicines was established to support the HSE in managing the significant amount of information on treatments for COVID-19. This COVID-19 Evidence Review Group is comprised of evidence synthesis practitioners from across the National Centre for Pharmacoeconomics (NCPE), Medicines Management Programme (MMP) and the National Medicines Information Centre (NMIC). The group respond to queries raised via the Office of the CCO, National Clinical Programmes and the Department of Health and respond in a timely way with the evidence review supporting the query.

Summary

Intravenous immunoglobulin is a pooled preparation of normal human Immunoglobulin G, used as replacement therapy for humoral immune disorders and for specified inflammatory diseases for patients with humoral immunodeficiency and certain neuroinflammatory conditions. Clinical opinion highlighted that pooled IVIG products will not contain specific antibodies to SARS-CoV2; any potential effect will be non-specific.

There is no robust evidence from randomised controlled, comparative clinical trials supporting the use of IVIG in patients with COVID-19. A number of descriptive, observational studies were retrieved following a literature search. Four studies specifically evaluated the role of IVIG in patients with COVID-19. However, given the observational, single-armed, open-label design there is considerable bias in the estimates of benefit derived from IVIG. In several other studies, IVIG was a component of a multiple treatment strategy and it is therefore highly uncertain which treatment was beneficial.

A number of published guidelines have recently included a reference to the use of IVIG in patients with COVID-19, and recommendations range from explicit advice against its routine use due to lack of evidence on its benefit, to use in clinical trials alone or for its use to be led by clinical expert input.

Other than its broad use as an anti-inflammatory agent at high doses, there is limited rationale for the use of IVIG in COVID-19. The prothrombotic effect of IVIG may be a cause for concern in patients with severe COVID-19 who may have elevated D-dimer levels. Whilst this agent is considered, in some circumstances, as an adjunctive treatment in sepsis, it is not routine treatment. There is a risk that use of IVIG as a rescue therapy would compromise the supply of IVIG to patients established on it for conditions where benefit has been demonstrated. Clinical opinion advises that IVIG should not be used without input from the multidisciplinary team and ideally, and any use should be restricted to a clinical trial setting.

Conclusion

Like many treatments proposed to treat this condition, intravenous immunoglobulin is unlicensed for the treatment of COVID-19. This Rapid Evidence Review finds that there is currently insufficient evidence to support the use of IVIG in the management of patients with COVID-19. In addition, both the European Society of Intensive Care medicine/Society of Critical Care Medicine and the National Institute for Health guidelines advise against the use of IVIG in the treatment of COVID-19.

Rapid Evidence Review

Introduction

Intravenous immunoglobulin is a pooled preparation of normal human Immunoglobulin G, used at standard doses in replacement therapy for humoral immune disorders and at high doses (2g/kg over several days) for specified inflammatory diseases for patients with humoral immunodeficiency and certain neuroinflammatory conditions. Licensed indications for IVIG include immune thrombocytopaenia purpura, chronic inflammatory demyelinating polyneuropathy, Kawasaki disease and Guillain Barre Syndrome.

The mode of action of IVIG in inflammatory disorders encompass a number of proposed mechanisms including: anti-idiotype antibodies, complement modulation, blockade of activating Fc gamma Rs, saturation of FcRn carrier proteins, upregulation of inhibiting Fc gamma Rs and anti-cytokine antibodies(1–3).

Intravenous immunoglobulin is not licensed for the treatment of COVID-19.

Rationale for use and potential mechanism of action of IVIG in COVID-19

An understanding of the pathophysiology of infection with SARs-CoV-2 is rapidly evolving and postulated mechanisms underlying the clinical spectrum of COVID-19 are forming the basis for therapeutic strategies. While these proposed mechanisms are frequently extrapolated from studies from other coronavirus disorders, there is no evidence of efficacy for IVIG in MERs and studies in SARs-CoV are inconclusive(3–5).

Clinical infection with COVID-19 is considered to consist of three phases: a starting phase encompassing the acquisition of the virus and subsequent viraemia; an accelerating/acute phase in a proportion of affected cases leading to a pneumonia or acute respiratory distress often associated with hyperinflammation(6), and a recovery phase. Proposed host immune responses during the SARs-CoV-19 infection include the inhibition of anti-viral interferon responses resulting in uncontrolled viral replication(7). The attendant influx of neutrophils and monocytes/macrophages results in hyper-production of pro-inflammatory cytokines.

Inflammatory responses to Anti-Spike-IgG (on the surface of SARs-CoV2) form the basis for the postulated positive effect of IVIG in treatment of COVID-19(7). The formation of these anti-S-Ig neutralising antibodies may promote pro-inflammatory monocyte/macrophage accumulation and the production of MCP-1 and Il-8 in the lungs. It is hypothesised that these pro-inflammatory

responses are mediated through the binding of the virus-anti-S-IgG complex to the Fc receptors (FcR) present on monocytes/macrophages, as FcR blockade reduces the production of inflammatory cytokines. In addition, the neutralising antibodies may trigger FcR-mediated inflammatory responses and cause severe lung injury, which may be related to a phenomenon known as antibody-dependent enhancement of viral infection(7). IVIG could theoretically therefore exert it's mechanism of action in COVID-19 by saturating the IgG recycling capacity of FcRn and reduce the levels of antiviral neutralising antibody. It could also competitively block the binding of Nab to other FcRs.

Intravenous immunoglobulin as a therapeutic option in COVID-19

IVIG in infectious diseases

It is not common practice to use IVIG in the setting of infectious disease (9). There is some evidence to support its use in CMV pneumonitis in the transplant setting, while rotavirus can also be treated in this manner. Evidence also exists to support the use of IVIG in toxic shock syndrome due to Group A streptococcus(1).

IVIG in sepsis

IVIG and a related product, IgM enriched immunoglobulin, have long been considered potential therapeutic options in sepsis(8,9). Whilst systematic reviews have suggested benefits, variable trial quality precludes widespread application of IVIG. Similarly, IgM enriched immunoglobulin seems to be associated with improved mortality, but the data is inconsistent. Their use is therefore not widely accepted.

IVIG in cytokine release syndromes

There is no published data demonstrating the efficacy of IVIG in the management of cytokine release syndromes.

Evidence on the use of IVIG in patients with COVID-19

There is no robust evidence from randomised controlled, comparative clinical trials supporting the use of IVIG in patients with COVID-19. The available evidence is limited to descriptive case reports, case series and retrospective cohort studies.

A number of case reports have described the use of IVIG in adult patients with COVID-19(10–12). Hu *et al* describe a 37 year old male with significant enlargement of the heart who tested

positive for coronavirus who was diagnosed with coronavirus fulminant myocarditis with cardiogenic shock and pulmonary infection(10). Following treatment with methylprednisolone and immunoglobulin, noradrenaline and a number of other therapies, the patient's symptoms improved and heart size returned to normal. LeVine *et al* reported on the first case of coronavirus infection in Bhutan who was empirically treated with IVIG in addition to a number of other agents, while Shi *et al* reported on the successful treatment of a patient with COVID-19 with plasma exchange followed by IVIG therapy(11,12).

A further 6 case reports describe the role of IVIG in patients with underlying conditions or post-transplant co-infected with COVID-19 who received IVIG as part of their management(13–18).

A determination of benefit cannot be assumed to be attributed to IVIG from these case reports given the confounding with other therapies administered simultaneously.

A number of observational studies have described either the clinical features, treatment interventions and/or outcomes for cohorts of patients treated for COVID-19 with multiple agents, in addition to IVIG (Table 1, Appendix 2). Four studies have specifically described the potential role of IVIG in patients with COVID-19, two peer-reviewed reports and two preprints (Table 1)(19–22).

Cao *et al* described the treatment of IVIG (0.3-0.5g/kg) in 3 patients with severe COVID-19, when added in to existing prescribed medications including antiviral agents, antibiotic therapy, and supportive care(19). They postulated that the progression of the disease was blocked by IVIG due to a temporal association with administration of IVIG and patient improvement, although this may be confounded by co-prescribed medications.

Xie *et al*, in a retrospective analysis investigated the effect of IVIG on the primary outcome of 28-day mortality, in a cohort of 58 patients with severe COVID-19, and the secondary outcomes of 14-day mortality, hospital length of stay (LoS), ICU LoS and use of mechanical ventilation (20). The cohort was stratified according to administration of IVIG within 48 hours of admission to ICU, and those initiated more than 48 hours after admission to ICU. A total of 23 of the 58 patients died within 28 days of admission, 7 in the ≤48 h group and 16 in the >48h group. There was a statistically significant difference in 28-day mortality between the two groups (p=0.009). The hospital LoS for the ≤48 h group was significantly shorter than in the >48h group (11.50 ±1.030 vs 16.96 ±1.620 days, p=0.0055), and ICU LoS for the ≤48 h group was also shorter than that of the > 48 h group (9.533±1.089 vs 13.50 ±1.632 days, p=0.0453). The proportion of patients requiring mechanical ventilation in the ≤48 h group was also statistically significantly lower than in the > 48 h group (6.67% vs 32.14%, p=0.016)(20). The results of this study should

be interpreted with caution. The cohort was initially stratified according to the use of IVIG within 24 hours of admission, not 48 hours, and this analysis demonstrated no significant statistical difference. The subsequent stratification by initiation of IVIG within 48 hours or >48 hours of admission resulted in the statistically significant findings presented. The *post hoc* analysis nature of these findings is associated with uncertainty as a pre-planned analysis was not incorporated into the study methods. In addition, there appears to be no adjustment made for differences between patients, and these differences between the two groups may reflect differences between patients rather than between treatment effects, and therefore the comparison between the groups will be biased.

In a cohort of 10 patients Zhou *et al (Pre-print)* investigated the impact of a dose escalation in corticosteroid and IVIG therapy to a higher dose regimen which resulted in reported benefits in key indicators including the $PaCO_2/FiO_2$ ratio and lymphocyte counts in 7 of 10 treated patients(21). In this study, it is not clear how patients were chosen to enrol, and patients were on a number of other treatments making it difficult to determine the contribution of individual treatment interventions. There is the potential that these patients improved with time rather than due to the change in dose of IVIG and corticosteroid.

Shao *et al* (22) *(Pre-print)* conducted a multicentre retrospective cohort study to determine the primary outcome of 28-day mortality and 60 day-mortality in a cohort of 325 patients with either severe or critical COVID-19 infection, of whom 174 patients received IVIG. There was no difference in the 28-day (p=0.872) or 60-day mortality (p=0.222), or survival time (p=0.225) between those received IVIG and those who did not. The authors claim that following an adjusted COX regression sub-group analysis that there was some evidence that early use of IVIG following admission and treatment with higher daily doses were associated with a greater curative effect(22). However, the analysis adjusted for baseline patient factors on admission alone, but not for differences that occurred after admission. Therefore, changes in patient clinical status following admission were not adjusted for, which may have contributed to factors influencing decision-making around initiation of IVIG or not. The analysis may also be biased due to the absence of adjustments for differences in other prescribed interventions or additional supportive measures between the two groups.

A further eight descriptive observational studies have reported the use of IVIG in patients with COVID-19 as a component of a multiple treatment strategy including antiviral therapy, corticosteroids, thymosin preparations, antibiotics, and antifungal agents, and supportive care (Appendix 1). The contribution of IVIG to patient progress and outcomes cannot be determined from these studies.

Table 1 – Summary of studies focussing on the role of IVIG in the treatment of COVID-19

Study Title (location)	Methodology	Population	Outcome assessed	Efficacy data	Reference
Peer-reviewed reports					
High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with Coronavirus Disease 2019 (China)(19)	Case series	Patients (n=3) were classified with severe COVID-19 following admission.	Impact of treatment interventions on a) haematological indices particularly % lymphocytes, b) inflammatory markers: ESR, HsCRP; c) liver transaminases; d) coagulation markers (incomplete data) & a number of others	Descriptive presentation of the effect of IVIG at a dose of 25g (0.3-0.5g/kg) daily for 5 days added added to existing prescribed medications including antiviral agents, antibiotic therapy and supportive care. Postulated that the addition of IVIG successfully blocked the progression of the disease cascade of COVID-19 as evidenced by clinical improvement shortly after administration resulting in normalising temperature (within 1-2 days), and respiratory function improvement (within 3-5 days). Improvements in % lymphocytes, ESR and CRP and O_2 saturation. Limitations: Small number of patients, confounding with other agents Comment from authors: Timing of IVIG may be best prior to development of overall systemic damage.	Cao W, Liu X, Bai T, Fan H, Hong K, Song H, *et al*. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with Coronavirus Disease 2019. Open Forum Infectious Diseases. 2020 Mar 21;ofaa102.
Effect of regular intravenous immunoglobulin therapy on prognosis of severe pneumonia in patients with COVID-1 (China) (20)	Case series	58 patients with severe COVID-19 admitted to ICU	Primary: 28-day mortality Secondary: 14-day mortality, hospital length of stay, ICU LoS; use of mechanical ventilation	58 patients retrospectively analysed and stratified according to administration of IVIG 20g within 48 hours of admission to ICU vs those initiated on IVIG therapy after >48 hours. Results: 11 patients (18.96%) required mechanical ventilation, 5 (8.62%) non-invasive mechanical ventilation, 6 (10.3%) invasive mechanical ventilation, and 2 (3.45%) high-flow oxygen aspiration. A total of 23 of the 58 patients died within 28 days of admission, 7 in the ≤48 h group and 16 in the > 48 h group. There was a statistically significant difference in 28-day mortality between the 2 groups (p=0.009). The hospital LoS for the ≤48 h group was significantly shorter than in the > 48 h group (11.50 ±1.030 vs 16.96 ±1.620 days, p=0.0055), and ICU LoS for the ≤48 h group was also shorter than that of the > 48 h group (9.533±1.089 vs 13.50 ±1.632 days, p=0.0453); proportion of patients requiring mechanical ventilation in the ≤48 h group was also significantly lower than in the > 48 h group (6.67% vs 32.14%, p=0.016). Limitations: Beneficial outcomes in this retrospective case series may be confounded by the co-administration of additional interventions including LMWH; the absence of adjustment for differences in patients between the 2 groups; the arbitrary	Xie Y, Cao S, Dong H, Li Q, Chen E, Zhang W, *et al*. Effect of regular intravenous immunoglobulin therapy on prognosis of severe pneumonia in patients with COVID-19. J Infect. 2020;

				assignment of initiation of IVIG at a selected time point following admission without accounting for changes in clinical status of patients leading to the potential decision to initiate IVIG	
Pre-print articles					
Short-Term Moderate-Dose Corticosteroid Plus Immunoglobulin Effectively Reverses COVID-19 Patients Who Have Failed Low-Dose Therapy (China)(21)	Descriptive observational retrospective study	10 patients initially treated with low-dose corticosteroid (40-80mg/day) & IVIG (10g/day) were escalated to 160mg/day corticosteroid and 20g/day IVIG (short-term)	Impact of dose escalation on PaO_2/FiO_2 ratio, % lymphocytes & pulmonary CT findings in patients with COVID-19 and clinical outcomes	Improvements were observed once patients were escalated in terms of improvements in pulmonary radiographic abnormalities (n=7), stable (n=2), 1 deteriorating. A number of complications were observed including acute liver dysfunction in 80%, acute renal dysfunction in 60% in addition to secondary pulmonary infection, acute MI, ARDS and multiple organ failure. Half of the cohort remained hospitalised at time of completion of the analysis, 50% were discharged and 1 patient had died. Limitations: observational, non-randomised; small sample; background agents on-going Pre-print – a number of typographical errors and misspellings	Zhou Z-G, Xie S-M, Zhang J, Zheng F, Jiang D-X, Li K-Y, et al. Short-Term Moderate-Dose Corticosteroid Plus Immunoglobulin Effectively Reverses COVID-19 Patients Who Have Failed Low-Dose Therapy [Internet]. MEDICINE & PHARMACOLOGY; 2020 Mar [cited 2020 Mar 25]. Available from: https://www.preprints.org/manuscript/202003.0065/v1
Clinical Efficacy of Intravenous Immunoglobulin Therapy in Critical Patients with COVID-19: A Multicenter Retrospective Cohort Study (China)(22)	Multicentre retrospective cohort study	325 patients with severe (68%) or critical (32%) COVID-19 of whom 174 received IVIG	Primary: 28-day mortality and 60-day mortality Secondary: Hospital LoS; ICU LoS; duration of mechanical ventilation	The IVIG group were older, had higher APACHII scores & SOFA scores, higher levels of total bilirubin, direct bilirubin, creatine, CRP, IL-6, & lactate, but lower platelets and lymphocyte count (all $P<0.05$), & decreased PaO2/FiO2 ($P=0.011$). There was no significant difference in 28-day and 60-day mortality between the IVIG group and non-IVIG group ($P=0.872$ and $P=0.222$, respectively), and no significant difference in survival time ($P= 0.225$). The in-hospital day & total duration of disease were longer in the IVIG group (both $P < 0.001$), consistent with the more serious initial condition of IVIG group. Subgroup analysis showed that only in the critical type patients IVIG could significantly decrease the inflammatory response, improve some organ functions, reduce the 28-day mortality rate, and prolong the survival time. The study showed that early use of IVIG (admission≤ 7 days) with high dose (>15 g/d) exhibited a more significantly curative effect. Limitations: Non-randomised assignment to an IVIG arm, retrospective analysis, subgroup analysis not protocol driven, COX model not adjusted for changes in clinical status of patients following admission	Shao *et al.* Clinical Efficacy of Intravenous Immunoglobulin Therapy in Critical Patients with COVID-19: A Multicentre Retrospective Cohort Study. Available from https://www.medrxiv.org/content/10.1101/2020.04.11.20061739v2

Paediatric use of IVIG

Zheng *et al* collected data on 25 children with COVID-19 to determine the effect of multiple therapeutic interventions on the alleviation of symptoms of whom two received IVIG (2g/kg) and corticosteroids (2mg/kg)(23). Of the two patients, one experienced an alleviation in symptoms while one did not.

The association between infection with SARs-CoV-2 and Kawasaki Disease (KD) began to emerge in early May 2020(24). The standard treatment for Kawasaki Disease involves administration of IVIG and aspirin(25). Two case reports describe the use of IVIG in children with COVID-19 where one 6 month old with classic KD was treated successfully with IVIG and low dose aspirin, and another patient was treated with a combination of IVIG and tocilizumab(26,27). One French case series has reported the successful use of IVIG in 17 children with suspected Kawasaki Disease at a dose of 2g/kg in combination with low dose aspirin(28).

Clinical Expert Opinion

IVIG is frequently perceived as a benign immunomodulator and this has led directly to its extensive and occasionally over-zealous off label use. Its use in the UK is subject to a national demand management program with panel oversight and strict indications(29). Pooled IVIG products will not contain specific antibodies to SARS-CoV2. Any potential effect will be non-specific. It is important that IVIG products are not confused with the use of convalescent plasma or proposed hyperimmune IgG products.

Other than its broad use as an anti-inflammatory agent at high doses, there is limited rationale for the use of IVIG in COVID-19. Whilst this agent is considered, in some circumstances, as an adjunctive treatment in sepsis, it is not routine treatment. There is a very real risk that widespread use as a rescue therapy in COVID-19 would compromise the supply to highly vulnerable patient groups with immunodeficiency and neuroinflammatory diseases.

It must not be used in the setting of COVID-19 without discussion by a multidisciplinary team that should include infectious diseases, haematology, critical care and where available clinical immunology.

Ideally, the use of IVIG should be restricted to clinical trial settings.

IVIG may be prothrombotic, and additionally, some preparations have been associated with renal impairment(30). This may be a further cause for concern in COVID-19 infection given that D-

dimer elevation is a marker for poor outcome, and the prothrombotic effect of IVIG may pose an additional risk in this clinical setting.

Guidelines

There is an increasing focus in the published literature on the use of convalescent plasma or hyperimmune immunoglobulin derived from the blood of patients who have recovered from COVID-19. However, a number of published guidelines have recently included a reference to the use of non-SARs-CoV-2 IVIG in patients with COVID-19. Extracts from international guidelines and local guidelines alluding to IVIG for COVID-19 are included in Table 3. The general consensus is that there is insufficient evidence to support its use.

Table 2 Observations and recommendations from published guidelines for IVIG in COVID-19

European Society of Intensive Care Medicine and the Society of Critical Care Medicine. **Surviving Sepsis Guidelines**(31) March 28th, 2020	**Recommendation 45**. In critically ill adults with COVID-19, suggest against the routine use of standard intravenous immunoglobulins (IVIG). (*Weak recommendation, low-quality evidence.)*
Infectious Disease Society of America (IDSA)(32) 11th April 2020	Intravenous immunoglobulin (IVIg) has been used as an adjuvant to treat a variety of pathogens either as a pooled product or in a concentrated more pathogen focused (hyperimmune) form. As the community from which a given batch of IVIg is derived from includes increasing numbers of individuals who have recovered from SARS-CoV-2, the possibility of protective antibodies being present in the pooled product is increased. However, the potential utility of IVIg for the treatment of SARS-CoV-2 is unknown at this time. Its use has been reported in a few patients with COVID-19 but studies are needed to determine if there may be a role for IVIg in the treatment of SARS-CoV-2
Mass General Hospital Guidelines(33) 8th May 2020	If IgG <400, consider IVIG at dose of 25 grams x1 (unclear benefit), Note: Titres against SARS-CoV-2 are likely to be low in the population *IVIG preparations would not currently be expected to have sufficient antibody titres against SARSCoV-2 to offer effective passive immunity.*
National Institute of Health (NIH)(34) 11th May 2020	***Non-SARS-CoV-2-Specific Intravenous Immune Globulin Recommendation:*** The COVID-19 Treatment Guidelines Panel recommends against the use of non-SARS-CoV2-specific intravenous immune globulin (IVIG) for the treatment of COVID-19, except in the context of a clinical trial. This should not preclude the use of IVIG when it is otherwise indicated for the treatment of complications that arise during the course of COVID-19.
Johns Hopkins ABX-Guide COVID-19 (35) 14th May 2020	**Intravenous immunoglobulin (IVIG)** • Proposed as an intervention in the setting of viral-induced lung injury/ARDS that appears to be due to disordered regulatory T cells with a hyperimmune response • Better characterized in influenza-related ARDS, but COVID-19 appears similar.

	• Pooled IVIG reduces immune responses through multiple mechanisms including lessening interrupting complement cascade, lessening activated CD4+ and cytotoxic CD8+ T cells. • No clinical trial data to back use
Chinese Guidelines for the management of Patients with COVID-19, 7th Edition(36)	A potential therapeutic measure for the treatment of severe or critical cases of COVID-19 in children.

On 27th March 2020, an NHS speciality guideline was published relating to the management of patients requiring immunoglobulin treatment during the coronavirus pandemic and management of supply(37). This document, developed by the Immunology and Allergy Clinical Reference Group, does not recommend the use of IVIG for the treatment of patients with COVID-19 infection.

On-going clinical trials

Two clinical trials have been registered on www.clinicaltrials.gov as of May 13th, 2020:

1. Polyvalent Immunoglobulin in COVID-related ARDS - NCT04350580
2. Convalescent plasma versus Human Immunoglobulin to treat COVID-19 – NCT NCT04381858

One clinical trial has been registered on the EU clinical trials site - A multicentre randomized, open-label parallel pilot study to evaluate safety and efficacy of high dose intravenous immune globulin plus standard medical treatment vs standard medical treatment alone – No. 2020-001696.

A significant number of other clinical trials have been registered worldwide to investigate the efficacy of a number of antiviral and immunomodulating drugs in the management of COVID-19 e.g. SOLDARITY (NCT04321616), DisCoVeRy (NCT04315948) and REMAP-CAP (NCT02735707). IVIG is not a treatment of interest in any of these trials.

Safety of IVIG

Administration of IVIG is associated with known adverse reactions that are generally mild, transient and reversible. The risk of adverse events increases with high doses and rapid rates of infusion particularly on first dose infusion. Prevention strategies include adequate patient hydration, slow rates of infusion followed by gradual increases, and premedication with paracetamol and/or anti-histamines(38). Additional risks at high doses include renal failure, thrombosis and aseptic meningitis. Anand *et al* recently described the treatment of two patients

with myasthenia gravis and COVID-19 with IVIG without thromboembolic complications(38), although the emerging evidence on the hypercoagulable nature of COVID-19 is an on-going cause for concern(38–40).

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Appendix 1 Summary of studies where IVIG was a component of multiple interventions

Study Title (location)	Methodology	Population	Outcome assessed	Efficacy data	Reference
Peer-reviewed reports					
Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. (China) (41)	Descriptive, single centre, retrospective study	Patients (n=99) analysed for epidemiological, demographic, clinical, and radiological features and laboratory data and outcomes reported.	Proportion of patients recovered, died or still in hospital at time of report.	Descriptive presentation of the effect of multiple interventions on clinical outcomes for all cases. At the time of report conclusion, 31% of patients had been discharged, 11% had died and the remainder were still in hospital. Patients were treated with antiviral agents (76%), antibiotic therapy (71%), antifungal agents (15%), corticosteroids (19%) and 27 patients (27%) were treated with IVIG. Limitations: Small patient numbers. The impact of the addition of IVIG to existing prescribed medications cannot be determined without access to individual patient level data.	Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet. 2020 Feb;395(10223):507–13
Clinical Characteristics of Coronavirus Disease 2019 in China (China)(42)	Descriptive, multicentre retrospective study	Patients (n=1099) across 552 centres	Composite of admission to ICU, use of mechanical ventilation and death.	The primary composite end point occurred in 67 patients (6.1%), including 5.0% who were admitted to the ICU, 2.3% who underwent invasive mechanical ventilation, and 1.4% who died. A total of n=144 (13.1%) patients received IVIG therapy on a background of antibiotic (58%), antiviral (36%), corticosteroid (19%) and antifungal therapies (2.8%). Limitations: The impact of the addition of IVIG to existing prescribed medications on the outcomes of the study cannot be determined	Guan, W. et al 2020. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 382, 1708–1720. https://doi.org/10.1056/NEJMoa2002032
Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centred, retrospective, observational study(43)	Single-centred, retrospective, observational study	Patients (n=52) critically ill with COVID-19 admitted to ICU	Clinical course, treatments and outcomes, comparison of survivors vs non-survivors – primary outcome 28 day mortality	32 (61.5%) patients had died at 28 days 32. 54% of the total cohort of patients received IVIG, 45% of survivors and 59% of non-survivors added into additional medications including antibiotics, antiviral agents, corticosteroids and vasoconstrictive agents. Limitations: Small patient numbers. The impact of the addition of IVIG to existing prescribed medications on study outcomes cannot be determined.	Yang, X. et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centred, retrospective, observational study. Lancet Respir Med. https://doi.org/10.1016/S2213-2600(20)30079-5
Clinical characteristics of novel coronavirus	Observational descriptive study	Patients (n=137) were analysed in terms of their baseline characteristics,	Proportion of patients recovered, died or still in	Descriptive presentation of the effect of multiple interventions on clinical outcomes for patients included in the analysis. At the time of report conclusion, 32% of patients had improved and were discharged, 12% had died and 56% were receiving on-	Liu K, Fang Y-Y, Deng Y, Liu W, Wang M-F, Ma J-P, et al. Clinical characteristics of novel

cases in tertiary hospitals in Hubei Province: China (China)(44)		clinical manifestations and laboratory data and treatments prescribed.	hospital at time of report.	going treatment. Patients were treated with antiviral agents (77%), antibiotic therapy (87%), systemic corticosteroids (29%) and 44 patients (32%) were treated with IVIG. Limitations: Small patient numbers. The impact of the addition of IVIG to existing prescribed medications cannot be determined without access to individual level data.	coronavirus cases in tertiary hospitals in Hubei Province: Chin Med J (Engl). 2020 Feb;1.
Clinical features of 85 Fatal Cases of COVID-19 from Wuhan: A Retrospective Observational Study(45)	Retrospective observational study (case series)	85 cases of COVID-19 admitted to 2 hospitals in Wuhan, all of whom died	Clinical characteristics	IVIG was administered to 45% of the patients included in the series on a background of co-prescribed antibiotic (91%), antiviral (92%), corticosteroids (77%), and interferon-2αβ. Limitations: non-comparative study, role of IVIG cannot be determined, all patients died	Du Y, Tu L, Zhu P, Mu M, Wang R, Yang P, et al. Clinical Features of 85 Fatal Cases of COVID-19 from Wuhan: A Retrospective Observational Study. Am J Respir Crit Care Med. 2020;
Pre-print articles					
Retrospective Analysis of Clinical Features in 101 Death Cases with COVID-19 (China)(46)	Descriptive, observational, retrospective study	Review of data on n=101 patients who died from COVID-19	N/A	Of this cohort of patients who died from COVID-19, 60% received antiviral therapy, 58% corticosteroids, 63% IVIG and 45% thymosin preparations. All received antibiotic therapy. Limitations: All patients in this cohort died and the response to any of the individual treatments prescribed cannot be determined.	Chen Ji, Fan H, Zhang L, Huang B, Zhu M, Zhou Y, et al. Retrospective Analysis of Clinical Features in 101 Death Cases with COVID-19 [Internet]. Intensive Care and Critical Care Medicine; 2020 Mar [cited 2020 Mar 31]. Available from: http://medrxiv.org/lookup/doi/10.1101/2020.03.09.20033068
Early and Critical Care in Severe Patients with COVID-19 in Jiangsu Province, China: A Descriptive Study (China)(47)	Descriptive, retrospective study	Descriptive analysis of 60 cases of severe COVID-19 attending 12 hospitals. Patients were stratified into an improvement group and a deterioration group and subsequently compared.	Effect of therapy allowed initial stratification into improvement group & deterioration group, and subsequent determination of outcome - interim analysis	Of the 60 patients, all patients received antiviral therapy (including arbidol#, lopinavir/ritonavir, interferon, ribavirin or oseltamivir), 95% received antibiotic therapy, 3% antifungal therapy, 57% glucocorticoid therapy and 47% IVIG. In the interim analysis at time of publication (following 4 weeks of data collection), no patients had died, 83% had improved, 13% had deteriorated. Limitations: Interim analysis, unable to determine the impact of the addition of IVIG to on-going therapy;	Huang M, Yang Y, Shang F, Zheng Y, Zhao W, Luo L, et al. Early and Critical Care in Severe Patients with COVID-19 in Jiangsu Province, China: A Descriptive Study. SSRN Journal [Internet]. 2020 [cited 2020 Mar 30]; Available

					from: https://www.ssrn.com/abstract=3546056
Clinical features and progression of acute respiratory distress syndrome in coronavirus disease 2019(48)	Retrospective case series	109 patients admitted with coronavirus infection and treated with a number of agents	Differences in clinical characteristics between COVID-19 patients with and without ARDS	Overall 53(48.6%0 of patients developed ARDS, of whom 49.1% died (compared to 8.9% non-ARDS patients). Overall 56% received IVIG added into antibiotics, antiviral and/or glucocorticoid therapy. No significant effect of antivirus, 233 glucocorticoid, or immunoglobulin treatment on survival in COVID-19 patients with 234 ARDS (all log-rank tests P >0.05). Limitations: Retrospective analysis, unable to determine the impact of the addition of IVIG to on-going therapy	Liu Y, Sun W, Li J, et al. Clinical features and progression of acute respiratory distress syndrome in coronavirus disease 2019. medRxiv. 2020:2020.2002.2017.20024166.

- Arbidol is an antiviral agent that is used predominantly in China and Russia (ethyl-6-bromo-4-[(dimethylamino)methyl]-5-hydroxy-1-methyl-2-[(phenylthio)methyl]-indole-3-carboxylate hydrochloride monohydra

Appendix 2

IVIG search strategy May 13th 2020

Source	Search
Pubmed	Search (((("coronavirus pneumonia" OR “COVID-19” OR “2019 novel coronavirus infection” OR “2019-nCoV” OR "SARSCoV2" OR "SARS-CoV2" OR SARSCov19 OR "SARS-Cov19" OR "SARSCov-19" OR "SARS-Cov-19"))) AND (("Immunoglobulins, Intravenous"[Mesh] OR "intravenous immunoglobulin" OR "intravenous immunoglobulins" OR IVIG OR "intravenous IG")
Google Scholar	allintitle: "coronavirus pneumonia" OR “COVID-19” OR “2019 novel coronavirus infection” OR “2019-nCoV” OR "SARSCoV2" OR "SARS-CoV2" OR SARSCov19 OR "SARS-Cov19" OR "SARSCov-19" OR "SARS-Cov-19" AND "intravenous immunoglobulin’’ OR ‘’IVIG’’ (since 2019)
LitCovid	"intravenous immunoglobulin’’ OR ‘’IVIG’’
MedRxiv/ BioRxiv	“COVID-19” OR “2019 novel coronavirus infection” OR “2019-nCoV” OR "SARSCoV2" OR "SARS-CoV2" OR SARSCov19 OR "SARS-Cov19" OR "SARSCov-19" OR "SARS-Cov-19"))) AND "intravenous immunoglobulin’’ OR ‘’IVIG’’
ClinicalTrials.gov	COVID-19 (synonyms 2019-nCoV, SARS-CoV-2, 2019 novel coronavirus, severe acute respiratory syndrome coronavirus 2) and intravenous immunoglobulin OR IVIG
EudraCT	COVID-19 (synonyms 2019-nCoV, SARS-CoV-2, 2019 novel coronavirus, severe acute respiratory syndrome coronavirus 2) and intravenous immunoglobulin OR IVIG