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INTRAVENOUS IMMUNOGLOBULIN PRESCRIBING IN THE INTENSIVE CARE UNITS OF THREE JRMS MILITARY HOSPITALS IN JORDAN: A RETROSPECTIVE CROSS-SECTIONAL STUDY

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ABSTRACT

Objective: This study will explore the prescribing pattern of IVIG (50mg/mL, 10mL vial) in three JRMS hospitals ICUs (Prince Ali Bin Al-Hussein Military Hospital (PABH), Princess Haya Bint Al-Hussein Military Hospital (PHBH), and Queen Rania Hospital for Children (QRHC)) during 2019–2022. In particular, the study will provide a description of consumption by year and hospital, will detail demographic profile of recipient interm of age and sex distribution, will characterize inter-institutional variation, and will assess how well the observed prescribing of IVIG in critical care settings is aligned to current evidence-based indications for use of IVIG, which then may be used collectively in order to inform stewardship programs in IVIG inside the JRMS network.

Methodology: A retrospective cross-sectional study will be used; Administrative Pharmacy dispensing data from 2019-2022 will be captured from the JRMS hospital information systems. All prescriptions of IVIG (50mg/mL, 10mL vial) made in the ICU at PABH, PHBH, QRHC will be accepted. The data to be collected will consist of a line item for each prescription with the prescription year, as well as the sex of the patient, the patient age (numerical age in years or neonatal), and the dispensing hospital. numerical descriptive statistical analysis will be used to count the occurrence of prescription, calculate the percentage distribution for each age group and to describe the positions for each sex. Regarding inter-hospital comparisons, absolute and relative frequencies will be used.

Results: A total of 347 IVIG prescription records were identified across the three intensive care units during the study period. Prescription volume increased from 62 records in 2019 to 117 in 2020 and 124 in 2021, before declining to 44 records in 2022. Queen Rania Hospital for Children (QRHC) accounted for the largest proportion of prescriptions (53.0%), followed by Princess Haya Bint Al-Hussein Military Hospital (PHBH) (23.9%) and Prince Ali Bin Al-Hussein Military Hospital (PABH) (23.1%). Neonates represented the largest recipient group (66.6% of all patients), with particularly high neonatal utilization at PABH (97.5%) and PHBH (81.9%). QRHC demonstrated the most diverse age distribution, including infants, toddlers, children, and adolescents. Male patients constituted 57.3% of all recipients. The increase in IVIG prescribing during 2020–2021 coincided with the COVID-19 pandemic and may reflect the use of IVIG for inflammatory conditions such as multisystem inflammatory syndrome in children (MIS-C) and severe COVID-19-related complications.

KEYWORDS: Intravenous Immunoglobulin (IVIG); Intensive Care Unit; Drug Utilization Study; Neonatal Care; Pediatric Critical Care; COVID-19; Medication Stewardship; Jordanian Royal Medical Services; Prescribing Patterns; Critical Care Pharmacotherapy.

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1. INTRODUCTION:

Intravenous immunoglobulin (IVIG) is a polyclonal preparation of antibodies obtained from pooled human plasma, and has been documented to have indications in immunodeficiency disorders and autoimmune diseases, as well as in some infectious syndromes. IVIG is used in intensive-care unit (ICU) settings, such as neonatal sepsis, hypogammaglobulinemia, Kawasaki disease, immune thrombocytopenia, Guillain–Barré syndrome and for off-label uses including in immunocompromised patients with sepsis. (1,2) The crucial need for careful prescribing is highlighted by a number of drawbacks to the use of donated plasma such as a low availability and high cost of product, as well as potential adverse effects including thromboembolism, hemolytic anemia and renal impairment. (3)

Formerly, IVIG was considered to be a valuable therapeutic option for the prevention and treatment of neonatal alloimmune diseases and neonatal sepsis in the neonatal period, although this use of IVIG has been heavily criticized in the light of systematic reviews. In the pediatric critical care setting, the most solid data to support IVIG utilization has come from Kawasaki disease and immune thrombocytopenia while the role of IVIG in pediatric sepsis and other inflammatory diseases continue to be studied. At the other end of the spectrum, IVIG has been proven as standard therapy for immune-mediated polyneuropathies and some autoimmune encephalitides, and there are fewer data supporting its use in septic shock. (7)

Jordan's Jordan Royal Medical Services (JRMS) is a network of tertiary and secondary hospitals that was created to serve military personnel and their families as well as civilians. The three hospitals: Prince Ali Bin Al-Hussein Military Hospital (PABH), Princess Haya Bint Al-Hussein Military Hospital (PHBH), and Queen Rania Hospital for Children (QRHC) are among this network main hospitals that collaborate to provide ICU services to a wide range of people from neonates to elderly adults. Although the use of IVIG is a very important therapeutic choice yet it is a very expensive product, to date no research identifies the use of IVIG in the JRMS network at the clinic level. Awareness of and familiarity with prescribing behavior in this institutional setting is vital to guiding stewardship measures, maximizing resources use, and using current attention to evidence-based guidelines to direct clinical practice. (8)

In this study, the consumption trend, demographic characteristics of the recipients of IVIG in the three aforementioned JRMS hospitals during 2019–2022 were analyzed in a retrospective cross-sectional manner and the preferences for the use of IVIG in different hospitals were described.

2. LITERATURE REVIEW:

IVIG became clinically available in early 1980s, first to treat primary immunodeficiency disorders (PIDs). Therapies based on its mechanism include several pathways on the inhibition of Fcγ receptor (FcγR), the neutralization of complement, the modulation of cytokines and some studies providing pathogen-specific antibodies. It was subsequently expanded to treat many other indications over the next decades and is now one of the most widely used biological agents worldwide, with its production estimated to be more than 150 metric tons of IgG annually in the world. (1)

IVIG has been well studied for its use as a neonatal sepsis prophylaxis and treatment in neonatal medicine. The landmark study International Neonatal Immunotherapy Study (INIS), comprising almost 3,500 neonates, showed there to be no overall significant benefit in supplemental IVIG when using it in suspected or proven neonatal infection on the final level of mortality or major disability, which ruled out widespread use of IVIG for this purpose. However, IVIG still has a well-established place in neonatal alloimmune thrombocytopenia (NAIT) and hemolytic disease of the fetus and newborn (HDFN) by inhibiting the destruction of blood cells via Fc receptor-mediated binding of antibody. (10)

Beneath the age of 18, the strongest evidence for the use of IVIG in an ICU setting is in children with Kawasaki disease. Studies with multiple large trials of IVIG infusions at higher doses (2g/kg) plus aspirin have been shown to decrease the incidence of coronary artery abnormalities from about 25% to less than 5%, a result supported by the American Heart Association recommendations and studies. Systematic studies have examined the use of IVIG in septic shock, toxic shock and necrotizing fasciitis and there is possible benefit for IVIG in streptococcal toxic shock; data on this use is limited and it's role is not recommended for the time being. (12)

The use of IVIG for acute (adult) critical care has been well studied in sepsis and septic shock. individual studies and meta-analyses have produced evidence of improved mortality using polyclonal IVIG (especially IgM) containing preparations, but the quality level has been graded as low to moderate and routine administration of IVIG in sepsis is not recommended at current Surviving Sepsis Campaign guidelines. IVIG on the other hand can be used as per guidelines by treating immune-mediated neuropathies like

Guillain–Barré syndrome (GBS) and chronic inflammatory demyelinating polyneuropathy (CIDP) which can result in respiratory dysfunction and autonomic disorders necessitating admission to the intensive care unit (ICU). (2)

There have been multiple countries' drug utilization studies on IVIG. Off-label use was common and high cost burden, neonatal indications and primary immunodeficiencies were the most frequent indications according to Saudi Arabian multi-center study (14). Equally, about one-third of IVIG prescriptions were not rationale with national eligibility criteria as identified in an audit in Australia whereby it is recognized the significance of institutional review process (3). Within the Middle Eastern context, similarly to the situation in the Jordanian Military Health Services (JMS), or any other military healthcare system in Jordan, no analyses have been reported to date that are directly comparable to the present study, creating a genuine evidence gap that is tackled within this present study.

3. METHODOLOGY:

3.1 Study Design and Setting: This is a retrospective cross sectional study of the drug utilization conducted in 3 Intensive care Units at Prince Ali Bin Al-Hussein Military Hospital (PABH) (a general military hospital) and Princess Haya Bint Al-Hussein Military Hospital (PHBH) (a military hospital having a wide range of clinical services) and Queen Rania Hospital for Children (QRHC) (a dedicated pediatric hospital) in the JRMS hospital network in Jordan. The study period was a total of 4 calendar years (January 2019 to December 2022).

3.2 Data Source and Variables: Information was retrieved for each hospital from the Pharmacy Dispensing Record of each hospital. The dosage form of the drug of interest was IVIG 50mg/mL 10mL vial. All the information entered in each prescription record was used and it included the following: Prescribing year, sex of the patient male/female, age of the patient in years or neonatal status if the patient was within the neonatal period, dispensing hospital.

3.3 Patient Classification: Patients were divided into five age group: neonates (those who were documented as newborns); infants (aged ≤1 year); toddlers (aged 2–5 years); children adolescents (aged 6–17 years) and adults (aged ≥ 18 years). The classification was adopted from the current developmental stage classifications of pediatric pharmacology studies which had been used to make meaningful, inter-institutional comparisons due to the wide differences in patient populations across the three hospitals.

3.4 Statistical Analysis: Throughout this study descriptive statistics were used. Categorical data (sex, age group, hospital, year) was presented as absolute frequency and percentages. The absolute differences and percentage changes in the number of prescriptions were obtained from year-on-year changes. Various comparisons were carried out between hospitals within the cluster, including age group distribution and sex distribution and discussed contextually based on the mission of each hospital. Since this is a descriptive utilization study, there was no inferential statistical testing applied.

4. RESULTS AND DISCUSSION:

4.1 Overall Volume and Temporal Trends: During a period of four years of study there were 347 prescription records for IVIG in the 3 hospitals. Table 1 shows the distribution of the prescriptions by hospital and year.

Table 1. IVIG Prescription Volume by Hospital and Year

Hospital	2019	2020	2021	2022	Total
PABH	13	27	34	6	80
PHBH	16	29	28	10	83
QRHC	33	61	62	28	184
Total	**62**	**117**	**124**	**44**	**347**

PABH = Prince Ali Bin Al-Hussein Military Hospital; PHBH = Princess Haya Bint Al-Hussein Military Hospital; QRHC = Queen Rania Hospital for Children

Prescribing volume rose markedly from 62 records in 2019 to 117 in 2020 (+88.7%) and further to 124 in 2021 (+6.0%), before declining sharply to 44 records in 2022 (−64.5%). This marked surge in the number of IVIG administrations in 2020, which was apparently prompted by the outbreak of the COVID-19 pandemic and the subsequent use of IVIG in some cases for inflammatory complications of COVID-19 such as Multi System Inflammatory Syndrome in children (MIS-C) and severe COVID-19 disease in adult

patients (15). A comparable episode of IVIG uptake during a pandemic has been reported elsewhere and is seen in the use for children with MIS-C, a condition with immunopathological characteristics common with Kawasaki disease, already known to be an indication for IVIG use (16). The large drop in 2022 most likely reflects the normalization of the increased prescribing during the pandemic, strengthening stewardship of dispensing, and potential "drug shortage" time periods (Figure 1).

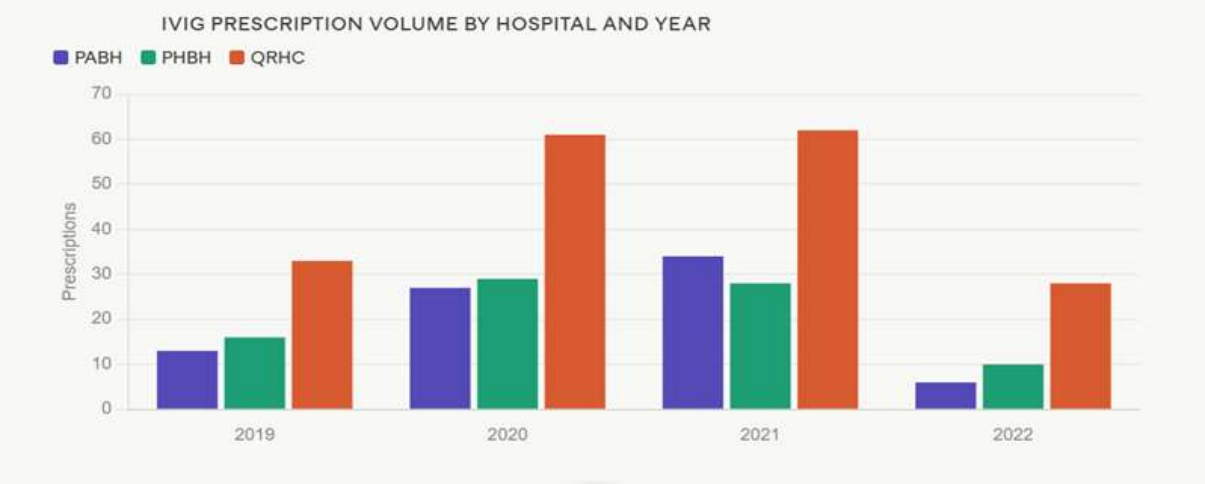

Figure 1: IVIG prescription volume by hospital and year

QRHC accounted for the largest share of prescriptions (184/347, 53.0%), followed by PHBH (83/347, 23.9%) and PABH (80/347, 23.1%). This distribution is like what one would expect to see in a dedicated pediatric tertiary center since the number of pediatric ICU admissions is expected to increase as is the number of IVIG prescriptions. The similar lower numbers at PABH and PHBH are due to the older adult weighted population due predominantly to military patients where IVIG is used in a more restricted range of indications.

4.2 Age Distribution and Inter-Hospital Case-Mix: The age profile of patients receiving IVIG was reported to be significantly different between institutions (Table 2) depending upon patient mandate in the different hospitals.

Table 2: Age Category Distribution of IVIG Recipients by Hospital

Hospital	Neonatal	Infant (≤1yr)	Toddler (2-5yr)	Child/Adol. (6-17yr)	Adult (≥18yr)	Total
PABH	78 (97.5%)	1 (1.3%)	0 (0%)	0 (0%)	1 (1.3%)	80
PHBH	68 (81.9%)	1 (1.2%)	6 (7.2%)	0 (0%)	8 (9.6%)	83
QRHC	85 (46.2%)	28 (15.2%)	28 (15.2%)	43 (23.4%)	0 (0%)	184
Total	**231 (66.6%)**	**30 (8.6%)**	**34 (9.8%)**	**43 (12.4%)**	**9 (2.6%)**	**347**

Adol. = Adolescent

It is interesting to note that across all hospitals combined, neonates made up the largest recipient group (231/347, 66.6%) indicating the main role played by neonatal intensive care units (NICUs), in JRMS network in relation to IVIG consumption. This is in line with the international literature that reports the neonates requiring the most IVIG in the hospital, mainly for these three indications: neonatal immune thrombocytopenia, alloimmune hemolytic disease and sepsis. (4,5)

Of the 80 people who received IVIG at PABH 78 (97.5%) received IVIG were neonates, suggesting that the majority of IVIG use was inside the NICU setting. The neonatal use accounts almost exclusively for IVIG use in this hospital as only one infant (≤1 year) and one adult (75-year-old male in 2021) received it. The tight focus on the neonates is internally coherent and may be considered in the context of prompting open discussion of the suitability of routine IVIG use in neonatal sepsis when not specifically indicated for an underlying immune disorder (5) (Figure 2).

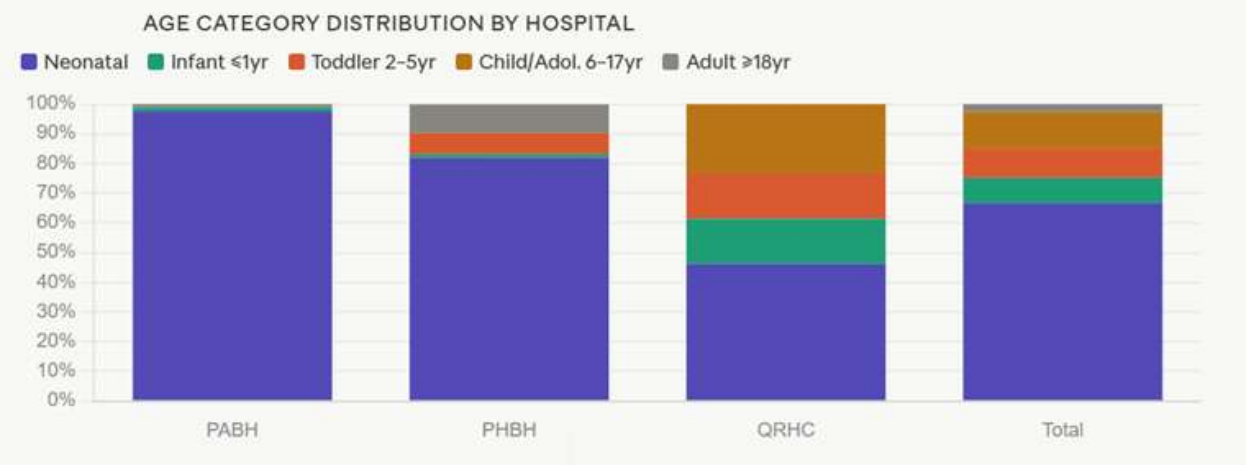

Figure 2: Age Category Distribution by Hospital

The majority of those who fell into the PHBH category was neonatal (81.9%, 68/83), with the remainder exhibiting a wide range of profiles. Interestingly, the 8 adult patients (9.6%) were the highest proportion of adult IVIG recipients in this hospital compared to the other 2 hospitals. The age of 45, 56, 58, 61 and 77 years for this adults recipients indicates that adult treatment of immune-mediated (or inflammatory) conditions may have been conducted in this facility. The current concentrations of adults in 2020 and 2021 could again be a reflection of the attention paid to prescribing for COVID-19 needs. (7,15)

QRHC exhibited the most diverse age group given it is a pediatric tertiary center. The hospital had a significant prescription volume for infants (15.2%, recipients 28/184), toddlers (15.2%, recipients 28/184) and children/adolescents (23.4%, recipients 43/184) with neonates still accounting for 46.2% (85/184) of all recipients. Specifically, the child and adolescent (6-17 years) patients of the QRHC have particular interest as they are the ones in whom these conditions are most likely to present Kawasaki disease, immune thrombocytopenic purpura (ITP) and pediatric autoimmune neurological conditions. It is further supported by multiple adolescent recipients being 15 years old (which was the majority on a female predominance, as occurred for autoimmune disorders like ITP and systemic lupus erythematosus) (12).

4.3 Sex Distribution: Table 3 presents the sex distribution of IVIG recipients across the three hospitals.

Table 3: Sex Distribution of IVIG Recipients by Hospital

Hospital	Male n (%)	Female n (%)	Total
PABH	43 (53.8%)	37 (46.3%)	80
PHBH	51 (61.4%)	32 (38.6%)	83
QRHC	105 (57.1%)	79 (42.9%)	184
Total	**199 (57.3%)**	**148 (42.7%)**	**347**

The male patients were outnumbered by females in all three hospitals (199 male, 57.3% vs. 148 female, 42.7%). This male predominance is similar to that observed in many other neonatal conditions, such as neonatal sepsis, respiratory distress syndrome and necrotizing enterocolitis for which IVIG can be used as adjunctive treatment in the NICU. The male preponderance in the critically ill neonate is a consistent finding and is believed to be related to difference in sex in surfactant production and maturation of immunity. (17)

The male to female ratio (61.4 to 38.6) was the highest in PHBH, which could partly reflect the patient population in the hospital (as the military population has a higher proportion of males compared to females). However, PABH showed a slightly more

even distribution of neonates, but skewed towards females, in some years, possibly due to random variation in a smaller number (Figure 3).

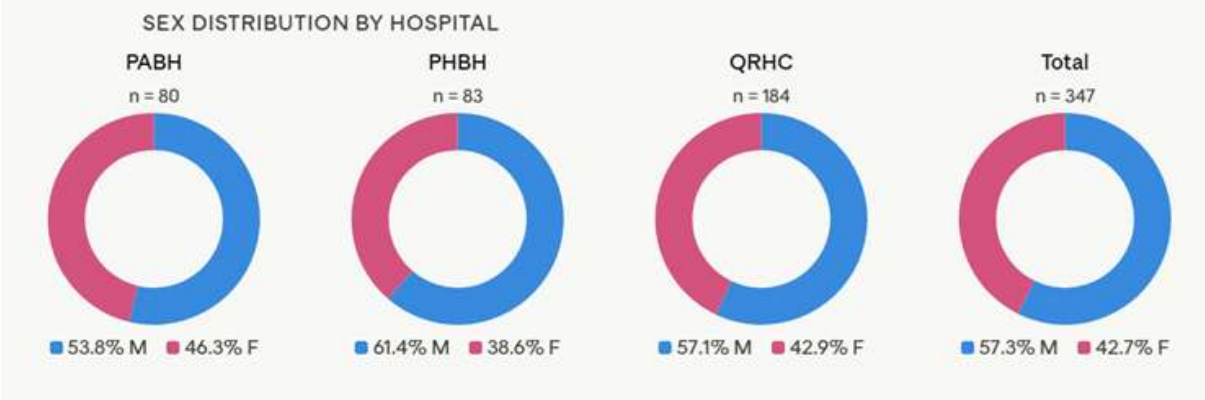

Figure 3: Sex distribution by age

A large group of female adolescent recipients (15 years) were evident at QRHC during 2021. This could be explained by autoimmune thrombocytopenias and other immune-mediated diseases more common among adolescent females such as cytopenias associated with systemic lupus erythematosus. However, to confirm this inference, future studies with clinical diagnostic information would be needed.

4.4 Inter-Hospital Prescribing Preferences and Stewardship Implications: Different case-mix observed between the hospitals may be commensurate with the distinct functions of the three hospitals rather than to their prescribing preferences. However, there are a few stewardship implications. IVIG prescription is almost exclusively used for neonates (97.5%) and thus a clinical audit to assess the following must be considered: is its use at PABH for neonatal indications (particular HDFN or alloimmune thrombocytopenia), for which evidence is strong, or is its use being expanded to routine neonatal sepsis prophylaxis for which evidence is less? (4,5,10)

The rise of adult IVIG prescriptions at PHBH (primarily during 2020–2021), suggests potential use for a pandemic context and should be assessed with prospective indication queries in future pharmacy systems. Randomly-administered IVIG has been documented in the region to be commonly used in adult ICUs but often lacking solid evidence to support it. (8,13)

However, QRHC's prescribing profile is diverse as one would expect for a pediatric tertiary center, and may be a result of guideline concordant use in a range of indications. Many of the cases of MIS-C reported during the 2020-2021 surge may have been linked to COVID-19, and treatment regimens for MIS-C cases have been reinforced by the use of IVIG after the initial report of COVID-19. Both gradual decrease in COVID-19 incidence (from COVID-19 pandemic to COVID-19 endemic) and enhanced triaging of IVIG prescribing after 2020-2021 event are suspected to account for the subsequent IVIG decrease seen at QRHC (from 62 to 28 prescriptions, −54.8%).

5. CONCLUSIONS:

A drug utilization study (DUS) of the use of IVIG in the three JRMS ICUs, conducted in a retrospective manner across the years 2019–2022, resulted in 347 prescription records. IVIG usage was skewed to neonates (66.6% of users) with PABH had a near near-exclusive neonatal prescribing (97.5% of those receiving the drug) while PHBH had a more varied age range including an adult population consistent with immune mediated conditions and QRHC had the widest age range, appropriate to its pediatric tertiary role. There was a significant increase in prescriptions during 2020–2021, which coincided with the COVID-19 pandemic, and may have been related to new inflammatory indications (such as MIS-C) during this time, followed by a return to normal prescribing in 2022. The distribution overall was more male patients than female (57.3%).

This information gives the first ever documentation of the use of IVIG in the JRMS network and will serve as a benchmark for future use of IVIG in these settings. The data illustrate the need to implement institutional stewardship tools: neonatal IVIG audits against evidence-based indications at PABH; prospective documentation of indications in all adult cases would improve future IVIG utilization review in PHBH; and incorporation of the clinical diagnosis codes into a

prospective manner in the pharmacy records would support evidence-alignment assessment in future studies across all three institutions. In conclusion, rational use of IVIG in an IVIG-scarce health service like JRMS network will need continuous monitoring, education for the health professionals and governance structures that are based on best evidence. (3,8)

REFERENCE:

1. Gelfand, E.W., 2012. Intravenous immune globulin in autoimmune and inflammatory diseases. *New England Journal of Medicine*, *367*(21), pp.2015-2025.
2. Perez, E.E., Orange, J.S., Bonilla, F., Chinen, J., Chinn, I.K., Dorsey, M., El-Gamal, Y., Harville, T.O., Hossny, E., Mazer, B. and Nelson, R., 2017. Update on the use of immunoglobulin in human disease: a review of evidence. *Journal of Allergy and Clinical Immunology*, *139*(3), pp.S1-S46.
3. Foreman, C., Russo, P., Davies, N., Hissaria, P., Proudman, S., Hughes, T. and Limaye, V., 2017. Use of intravenous immunoglobulin therapy for myositis: an audit in South Australian patients. *Internal Medicine Journal*, *47*(1), pp.112-115.
4. Ohlsson, A. and Lacy, J., 2004. Intravenous immunoglobulin for preventing infection in preterm and/or low birth weight infants. *Cochrane database of systematic reviews*, (1).
5. INIS Collaborative Group, 2011. Treatment of neonatal sepsis with intravenous immune globulin. *New England Journal of Medicine*, *365*(13), pp.1201-1211.
6. Newburger, J.W., Takahashi, M. and Burns, J.C., 2016. Kawasaki disease. *Journal of the American College of Cardiology*, *67*(14), pp.1738-1749.
7. Alejandria, M.M., Lansang, M.A.D., Dans, L.F., Mantaring III, J.B. and Cochrane Emergency and Critical Care Group, 1996. Intravenous immunoglobulin for treating sepsis, severe sepsis and septic shock. *Cochrane Database of Systematic Reviews*, *2018*(12).
8. Alangari, A.A., Abutaleb, M.H., Albarraq, A.A. and Al-Dhowailie, A.A., 2008. Intravenous immunoglobulin utilization in a tertiary care teaching hospital in Saudi Arabia. *Saudi Med J*, *29*(7), pp.975-9.
9. Schwab, I. and Nimmerjahn, F., 2013. Intravenous immunoglobulin therapy: how does IgG modulate the immune system?. *Nature Reviews Immunology*, *13*(3), pp.176-189.
10. Winkelhorst, D., Murphy, M.F., Greinacher, A., Shehata, N., Bakchoul, T., Massey, E., Baker, J., Lieberman, L., Tanael, S., Hume, H. and Arnold, D.M., 2017. Antenatal management in fetal and neonatal alloimmune thrombocytopenia: a systematic review. *Blood, The Journal of the American Society of Hematology*, *129*(11), pp.1538-1547.
11. McCrindle, B.W., Rowley, A.H., Newburger, J.W., Burns, J.C., Bolger, A.F., Gewitz, M., Baker, A.L., Jackson, M.A., Takahashi, M., Shah, P.B. and Kobayashi, T., 2017. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *circulation*, *135*(17), pp.e927-e999.
12. Papadopoulou-Alataki, E., Hassan, A. and Davies, E.G., 2012. Prevention of infection in children and adolescents with primary immunodeficiency disorders. *Asian Pacific Journal of Allergy and Immunology*, *30*(4), p.249.
13. Rhodes, A., Evans, L.E., Alhazzani, W., Levy, M.M., Antonelli, M., Ferrer, R., Kumar, A., Sevransky, J.E., Sprung, C.L., Nunnally, M.E. and Rochwerg, B., 2017. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive care medicine*, *43*(3), pp.304-377.
14. Alkhuwaiter, R.A., Alghasham, Y.A., Alharbi, M.M., Almoutiri, A.M., Alharbi, T.Y., Alaqeel, S.A., Alosaily, Y. and Alrasheed, A.M., 2026. A retrospective study on the use of immunoglobulin therapy in pediatric patients: Indications, dosage, and side effects in the Qassim Region, Saudi Arabia. *Saudi Journal for Health Sciences*, *15*(1), pp.41-45.
15. Dimopoulos, G., de Mast, Q., Markou, N., Theodorakopoulou, M., Komnos, A., Mouktaroudi, M., Netea, M.G., Spyridopoulos, T., Verheggen, R.J., Hoogerwerf, J. and Lachana, A., 2020. Favorable anakinra responses in severe Covid-19 patients with secondary hemophagocytic lymphohistiocytosis. *Cell host & microbe*, *28*(1), pp.117-123.
16. Henderson, Lauren A., Scott W. Canna, Kevin G. Friedman, Mark Gorelik, Sivia K. Lapidus, Hamid Bassiri, Edward M. Behrens et al. "American College of Rheumatology clinical guidance for multisystem inflammatory syndrome in children associated With SARS–CoV-2 and hyperinflammation in pediatric

COVID-19: version 1." *Arthritis & Rheumatology* 72, no. 11 (2020): 1791-1805.

and fall of excess male infant mortality. *Proceedings of the National academy of Sciences*, *105*(13), pp.5016-5021.

CONFLICT OF INTEREST REPORTED: NIL; SOURCE OF FUNDING: NONE REPORTED

17. Drevenstedt, G.L., Crimmins, E.M., Vasunilashorn, S. and Finch, C.E., 2008. The rise