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The Sri Lanka Prescriber

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Medications Used in Ovulation Induction in Fertility Practice

Introduction

Ovulation induction plays an important step in managing infertility, particularly in anovulatory conditions such as polycystic ovary syndrome (PCOS). Ovulation induction agents stimulate the development and release of a mature oocyte, thereby enhancing the chances of natural conception or improving the efficacy of assisted reproductive technologies (ART). This article reviews the commonly used medications in ovulation induction, including selective oestrogen receptor modulators (SERMs), aromatase inhibitors, gonadotrophins, GnRH analogs, adjuvant therapies such as metformin and dexamethasone, and emerging treatments. Regional challenges and strategies for low-resource settings, especially in Sri Lanka, are also discussed.

1. Selective Oestrogen Receptor Modulators (SERMs)

Clomiphene Citrate (CC)

Clomiphene citrate has remained the mainstay of ovulation induction since its introduction in the 1960s. As a selective oestrogen receptor modulator (SERM), it binds to oestrogen receptors in the hypothalamus, blocking negative feedback and stimulating the release of gonadotrophin-releasing hormone (GnRH). This leads to increased secretion of follicular stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary, leading to follicular development.

Effectiveness: Ovulation is achieved in 70–80% of cases, with pregnancy rates around 35–40% after six cycles [1].

Limitations:

- Around 20–25% of women may be CC-resistant (fail to ovulate)
- Anti-oestrogenic effects on endometrium and cervical mucus can impair implantation
- Associated with multiple gestation (8–10%) [1]

Tamoxifen

Tamoxifen, another SERM primarily used in breast cancer treatment, can induce ovulation in a mechanism similar to CC. It is less commonly used

but offers a viable alternative in certain clinical scenarios.

Advantages:

- Fewer anti-oestrogenic effects on the endometrium
- Better cervical mucus profile
- Suitable for women with thin endometrial lining while on CC

In low-resource settings where newer agents may be inaccessible, it can be a cost-effective second-line agent.

2. Aromatase Inhibitors

Letrozole

Letrozole is a third-generation aromatase inhibitor that suppresses peripheral oestrogen production by blocking the conversion of androgens to oestrogen. This leads to decreased oestrogen levels, which in turn increases FSH secretion through feedback mechanisms at the hypothalamic-pituitary axis. It has been used as a first line drugs in women with PCOS.

Advantages:

- Higher pregnancy and live birth rates compared to CC, particularly in PCOS [2]
- Minimal anti-oestrogenic effect on endometrium and cervical mucus
- Tends to induce mono-follicular development, lowering the risk of multiple gestations

Extended Use of Letrozole:

For women who do not respond adequately to the standard 5-day letrozole regimen, particularly those with CC resistance, obesity, or slow follicular growth, extended letrozole protocols is an effective alternative. Prolonged suppression of oestrogen maintains FSH stimulation for longer periods, allowing more time for follicular development.

Benefits:

- Improved follicular recruitment
- Higher ovulation and clinical pregnancy rates
- Enhanced endometrial thickness

Evidence: A study by Mitwally and Casper (2005)[3] demonstrated that extended letrozole regimens improved ovulatory response in women who were anovulatory due to PCOS or CC resistance.

Table 1: Comparison between Letrozole and Clomiphene Citrate

Characteristics	Letrozole	Clomiphene citrate
Ovulation rate	~75–80%	~70–80%
Pregnancy rate	Higher	Lower
Endometrial effect	Neutral/positive	Thinning
Cervical mucus	Favorable	Unfavorable
Risk of multiple pregnancies	Lower	Higher
Use in CC resistance	Often effective	Ineffective

Due to its superior efficacy and safety profile, letrozole is now recommended by both the American Society for Reproductive Medicine (ASRM) and European Society of Human Reproduction and Embryology (ESHRE) as the first-line agent for ovulation induction in PCOS women [2]. A comparison of the effects of CC and letrozole is given in Table 1.

3. Gonadotrophins

Gonadotrophins are injectable hormonal preparations containing FSH and, in some formulations, LH. They are used for ovulation induction in women who do not respond to oral agents or as part of controlled ovarian hyperstimulation (COH) in intrauterine insemination (IUI) and *in-vitro* fertilization (IVF) protocols.

Gonadotrophins act directly on the ovaries by stimulating the granulosa cells (via FSH) and theca cells (via LH) to promote:

- Recruitment and growth of ovarian follicles
- Estradiol production
- Follicular maturation
- Preparation of the endometrium for implantation

The administration of exogenous FSH bypasses the hypothalamic-pituitary axis, making it effective in women with hypothalamic amenorrhea or pituitary dysfunction, as well as in clomiphene/letrozole-resistant PCOS patients.

Types of Gonadotrophins

1. Urinary-Derived Gonadotrophins:

- hMG (Human Menopausal Gonadotrophin): Contains both FSH and LH activity
 - Urinary FSH: Highly purified FSH with minimal LH content
2. Recombinant Gonadotrophins:
- Recombinant FSH: Pure, consistent dosing, but more expensive
 - Recombinant LH: Added when needed for women with low endogenous LH

Gonadotrophin regimens must be carefully used to prevent ovarian hyperstimulation syndrome (OHSS) and multiple gestations.

Total Doses and Duration:

- Typically requires 6–12 days of injections.
- Total dose ranges from 600–1500 IU depending on ovarian reserve and response
- Individualized based on age, anti-mullerian hormone (AMH), body mass index (BMI), and ovarian reserve testing

Monitoring:

- Ultrasound: To track number and size of follicles (aim: 1–2 dominant follicles in IUI cycles)
- Serum estradiol (E2): Helps assess response and predict ovarian hyperstimulation syndrome (OHSS) risk
- Endometrial thickness: Should be >7 mm before triggering ovulation

Indications for Gonadotrophin Therapy:

- Clomiphene/Letrozole-resistant PCOS
- Hypogonadotrophic hypogonadism
- Unexplained infertility after failure of oral agents

- Ovulation induction prior to IUI
- Controlled ovarian stimulation for IVF
- Diminished ovarian reserve, requiring higher doses in ART

Efficacy and Success Rates:

- Ovulation Rates: >90% in responsive women
- Pregnancy Rates:
 - o In ovulation induction + timed intercourse: ~15–25% per cycle
 - o In IUI cycles: 15–20% per cycle
 - o In IVF cycles: 30–45% per cycle (age-dependent)
- Multiple Pregnancy Risk:
 - o Monitored cycles: ~10–20%
 - o Unmonitored or high-dose protocols: higher risk
- Live Birth Rates: Depend on indication and number of follicles; higher in IVF when used with embryo transfer

Evidence to Support:

- Studies have established gonadotrophins as highly effective second-line therapy after oral agent failure
- A meta-analysis by Fauser et al. (2011) emphasized their role in women with anovulatory infertility and normo-ovulatory women undergoing ART [4]

Challenges:

- High cost of recombinant preparations
- Requirement for ultrasound and laboratory monitoring
- Storage issues (cold chain for rFSH)

Strategies:

- Use urinary gonadotrophins (e.g., hMG or uFSH) to reduce cost
- Use low-dose protocols to prevent OHSS and minimize monitoring frequency

4. GnRH Agonists and Antagonist

GnRH Agonists

GnRH agonists initially stimulate FSH/LH release (flare effect), then suppress gonadotrophins via downregulation of pituitary GnRH receptors. Used to prevent premature LH surges in IVF protocols [4].

Examples: Leuprolide acetate, Buserelin

Use: Long protocols for IVF; ovulation triggering in high-responder patients to reduce OHSS risk.

GnRH Antagonists

Antagonists bind directly to GnRH receptors, resulting in immediate suppression of gonadotrophin release.

Examples: Cetrorelix, Ganirelix.

Use: Short protocols; offer more flexibility and lower OHSS risk.

5. Human Chorionic Gonadotrophin (hCG)

Human chorionic gonadotrophin (hCG) is routinely used in ovulation induction protocols to mimic the natural mid-cycle luteinizing hormone (LH) surge. It facilitates the final maturation of the dominant follicle and triggers ovulation, typically within 36–40 hours after administration.

Mechanism of Action

hCG is structurally similar to LH and binds to the LH/hCG receptor on the granulosa and theca cells of the pre-ovulatory follicle. Its effects include:

- Resumption of oocyte meiosis (from metaphase I to metaphase II)
- Expansion of cumulus cells
- Luteinization of granulosa cells
- Follicular rupture and oocyte release from the dominant follicle

In assisted reproduction, hCG is administered once the lead follicle reaches 18–20 mm in diameter and adequate endometrial thickness is achieved (>7 mm).

Dosing Options:

- Urinary hCG (u-hCG): 5,000–10,000 IU intramuscularly
- Recombinant hCG (r-hCG): 250 mcg subcutaneously
- Low-resource option: u-hCG is widely available and cost-effective, often used in public sector facilities and low-resource settings

Benefits:

- Reliable ovulation trigger: Ovulation occurs in ~90% of women within 36–40 hours after administration
- Timed interventions: hCG administration allows for precise scheduling of timed intercourse,

intrauterine insemination (IUI), or oocyte retrieval in ART

- Optimized luteal phase support: It induces luteinization of the ruptured follicle, supporting progesterone production from the corpus luteum

Success Rates and Efficacy:

- In women with anovulatory infertility undergoing ovulation induction with oral agents (CC or letrozole), hCG increases the probability of ovulation and timed conception when compared to spontaneous LH surge tracking
- Studies show that hCG-triggered cycles in women using CC or letrozole have pregnancy rates of 12–18% per cycle, depending on age, follicle count, and timing of intercourse or IUI
- In IUI cycles, pregnancy rates may reach 15–20% per cycle when hCG is used to synchronize insemination with ovulation
- It is particularly useful in women with suboptimal endogenous LH surges, including those with hypothalamic amenorrhea or luteal phase defects

Risks and Considerations:

- Ovarian Hyperstimulation Syndrome (OHSS): hCG can exacerbate OHSS in women with multiple follicles or PCOS. Alternative triggers like GnRH agonists may be preferred in high responders
- Luteal phase support: In some ART protocols, hCG may be followed by progesterone supplementation to support early implantation

Use in Low-Resource Settings:

- Urinary hCG is inexpensive, effective, and widely available in pharmacies and public hospitals across Sri Lanka.
- It remains the most practical option for ovulation triggering in low-cost infertility care, particularly when monitoring infrastructure is limited.

6. Adjuvant Treatments

Metformin

Metformin, an insulin sensitizer, is widely used in PCOS women with insulin resistance.

Mechanism: Reduces hepatic glucose output and improves peripheral insulin sensitivity, which in turn lowers androgen production and restores ovulation.

Evidence: A Cochrane review by Tang et al. (2012) confirmed that metformin, when used alone or with CC, improves ovulation and pregnancy rates in PCOS [5].

Advantages:

- Useful in obese women and those with metabolic syndrome
- Low cost and oral route make it ideal in low-resource settings

Dexamethasone

Dexamethasone is used to suppress adrenal androgens in hyperandrogenic women, especially when dehydroepiandrosterone sulfate (DHEA-S) is elevated.

Mechanism: Reduces adrenocorticotrophin hormone (ACTH) secretion, decreasing adrenal androgen production.

Evidence: A randomized study by Elnashar et al. (2006) demonstrated that addition of dexamethasone to CC significantly improved ovulatory response in CC-resistant PCOS women [6].

7. Emerging and Investigational Therapies

Kisspeptin Agonists

These agents stimulate natural GnRH release and are being explored as safer alternatives to hCG for ovulation triggering, especially in high-risk OHSS patients.

Inositol Supplements

Myo-inositol and D-chiro-inositol are insulin sensitizers that may help restore ovulation in PCOS.

Benefits: Improved menstrual regularity, follicular development, and metabolic profile.

8. Strategies for Ovulation Induction in Low-Resource Settings

In low- and middle-income countries (LMICs) such as Sri Lanka, infertility management often faces unique challenges due to limited access to advanced diagnostics, expensive medications, and specialized

fertility centers. However, effective ovulation induction strategies can still be implemented by optimizing available resources and focusing on affordable, evidence-based care. The following are practical, context-specific approaches:

1) Prioritize Oral Agents Over Injectables

- Letrozole and CC should be first-line treatments. They are orally administered, relatively inexpensive, and widely available
- Letrozole is increasingly replacing CC as the preferred agent due to better pregnancy outcomes, but cost and availability may limit its use in rural areas
- Tamoxifen offers a useful alternative when CC or letrozole is contraindicated or unavailable

2) Use of Extended Protocols

- Extended letrozole regimens (7–10 days) can be used in women who do not respond to standard 5-day dosing, offering a cost-effective alternative to gonadotrophins
- This can delay or even eliminate the need for expensive injectable stimulation

3) Combine with Low-Cost Adjuvants

- Metformin is affordable and widely available in government hospitals and pharmacies. It improves ovulation in PCOS, particularly in obese or insulin-resistant women
- Dexamethasone is also inexpensive and can be used in women with hyperandrogenism or CC resistance, improving ovulatory response
- These oral agents can be used alongside CC or letrozole without significantly increasing treatment costs

4) Timed Intercourse Education

- Many couples are unaware of the fertile window. Providers should counsel patients on timing intercourse relative to expected ovulation to maximize chances of conception.
- Cycle tracking and ovulation predictor kits can enhance patient autonomy in this regard

5) Limit Use of Gonadotrophins

Injectable gonadotrophins should be reserved for:

- Documented CC/letrozole resistance after combination therapies
- Patients undergoing ART in well-equipped tertiary care settings
- Where necessary, use low-dose step-up regimens with strict monitoring to minimize costs and risks (especially OHSS)

6) Consider Low-Cost IUI Protocols

- For couples with mild male factor or unexplained infertility, oral stimulation (letrozole or CC) plus IUI is a relatively affordable and effective strategy compared to IVF
- Many private and semi-government fertility centers in Sri Lanka offer IUI at lower costs than IVF

7) Encourage Public-Private Collaboration

- Strengthening referral systems from base hospitals to tertiary fertility centers (e.g., Castle Street Hospital for Women, Kandy General Hospital) can ensure continuity of care
- Establishing regional fertility outreach clinics can reduce travel and improve accessibility

8) Improve Provider Training

- General practitioners and gynecologists should be trained in basic infertility evaluation and management, including ovulation induction protocols
- This decentralizes care and reduces patient backlog at major centers

9) Patient Support and Education

- Cultural stigma and psychological distress are major barriers to care-seeking
- Educating patients on infertility as a medical condition and offering community-based counseling services can improve engagement and adherence

Conclusion

Ovulation induction remains a central and evolving component of infertility treatment, especially for women with anovulatory disorders such as PCOS. As supported by strong clinical evidence, the therapeutic landscape has shifted over the past two decades, with letrozole now emerging as the first-line

agent in many guidelines due to its superior outcomes. The landmark randomized controlled trial by Legro et al. (2014) demonstrated that letrozole had higher live birth rates and fewer adverse effects than CC in women with PCOS, solidifying its place in routine practice [2].

Despite CC's widespread historical use and accessibility, its anti-oestrogenic effects on the endometrium and cervical mucus may compromise implantation and contribute to suboptimal pregnancy rates, particularly in resistant populations. Nevertheless, in low-resource settings, CC remains an important first-line option due to its affordability and ease of administration [1]. In such contexts, extended letrozole protocols, as shown by Mitwally and Casper (2005), provide a useful alternative before advancing to more expensive injectable gonadotrophins [3].

Metformin, according to the Cochrane review by Tang et al. (2012), has proven effective in improving ovulation and pregnancy rates in women with insulin resistance and PCOS, especially when combined with CC [5]. This highlights the importance of addressing the metabolic component of ovulatory dysfunction, particularly in obese or insulin-resistant patients. Similarly, dexamethasone has shown benefits in CC-resistant cases by suppressing adrenal androgens, as evidenced by Elnashar et al. (2006), making it a low-cost and valuable adjunct therapy in select hyperandrogenic patients [6].

For women who do not respond to oral agents or have complex infertility profiles, gonadotrophins and GnRH analogs offer more precise follicular control but come with higher costs, greater risks (e.g., OHSS), and the need for intensive monitoring [4]. Their use is generally limited to tertiary or private fertility centers, especially in countries like Sri Lanka where resource constraints exist.

A key take-home message from the available evidence is the value of individualized treatment. No single protocol fits all patients, and success depends on tailoring treatment based on patient characteristics, availability of medications, and healthcare infrastructure. In low-resource settings, combining oral agents (letrozole or CC) with affordable adjuncts (metformin, dexamethasone) and

simplified monitoring strategies can significantly improve access and outcomes for infertile couples.

Case Scenario 1: Clomiphene Resistance in PCOS

A 28-year-old woman with a 3-year history of primary infertility is diagnosed with PCOS based on Rotterdam criteria. BMI is 32 kg/m². She has completed 3 cycles of CC 150 mg/day for 5 days without ovulation. Laboratory tests reveal insulin resistance; DHEA-S levels are mildly elevated.

Pre-treatment plan:

- Initiate metformin 500 mg/day, titrate to 1500 mg/day over 3 weeks.
- Add dexamethasone 0.25 mg at bedtime for 10 days starting from day 1 of the cycle.

Ovulation induction:

- Letrozole 5 mg/day from cycle day 2–6.
- Ultrasound monitoring from day 9.
- Trigger ovulation with 5000 IU urinary hCG when dominant follicle reaches ≥ 18 mm.

Rationale:

- Letrozole is effective in CC-resistant PCOS.
- Metformin addresses insulin resistance; dexamethasone suppresses adrenal androgens

Case Scenario 2: Low-Resource Setting Gonadotrophin Use

A 34-year-old woman with 5-year secondary infertility, regular cycles, and unexplained infertility has failed 6 cycles of letrozole/IUI. She lives in a rural area with limited monitoring facilities.

Plan:

- Use urinary hMG 75 IU/day in a low-dose step-up regimen.
- Ultrasound at baseline, day 7, and day 11.
- Trigger with urinary hCG when 1–2 follicles reach ≥ 18 mm.
- Timed intercourse within 36 hours.

Rationale:

- Urinary hMG is cost-effective and widely available in Sri Lanka.
- Low-dose step-up minimizes risk of OHSS and multiple gestations.

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Self- assessment questions - Medications Used in Ovulation Induction in Fertility Practice

1. Regarding clomiphene citrate
 - A. It is a first-line agent in ovulation induction in PCOS.
 - B. It has anti-oestrogenic effects on the endometrium.
 - C. Resistance is defined as failure to conceive after 6 cycles.
 - D. Multiple pregnancy risk is higher than with letrozole.
 - E. It improves cervical mucus quality.
2. Letrozole use in ovulation induction
 - A. It is an aromatase inhibitor.
 - B. It improves endometrial thickness compared to CC.
 - C. It should not be used in CC-resistant women.
 - D. It reduces multiple pregnancy risk compared to CC.
 - E. Standard dosing is 2.5–7.5 mg/day for 5 days.
3. In low-resource settings
 - A. Metformin is an affordable adjuvant.
 - B. Extended letrozole regimens can be used in CC resistance.
 - C. Gonadotrophins should be first-line agents.
 - D. Tamoxifen is a viable alternative when CC and letrozole are unavailable.
 - E. Low-cost IUI protocols can be effective for mild male factor infertility.

Self- assessment – Answers

1. FTFTF

Letrozole should be the first-line oral agent in PCOS (True).

Its anti-oestrogenic action can thin the endometrium (True).

Resistance refers to failure to ovulate (not failure to conceive) after up to three cycles at 150 mg/day (False).

Compared with letrozole, CC has a higher risk of multiple pregnancy (True).

CC adversely affects cervical mucus (False statement -that it improves it).

2. TTFTT

Letrozole is an aromatase inhibitor (True) and generally yields a more favorable endometrium than CC (True).

It is effective in many CC-resistant women, so saying it should not be used is incorrect (False).

Letrozole is associated with a lower multiple pregnancy risk than CC (True).

Standard dosing is 2.5–7.5 mg daily for 5 days (True).

3. TTFTT

Metformin is inexpensive and accessible, making it a useful adjuvant in PCOS (True).

Extended letrozole protocols are a practical option in CC resistance before injectables (True).

Gonadotrophins are not first line in resource-limited settings due to cost/monitoring needs (False).

Tamoxifen can be a reasonable alternative when CC/letrozole are unavailable or contraindicated (True).

Oral stimulation plus low-cost IUI can be effective for mild male factor/unexplained infertility (True)

Human Normal Immunoglobulin - National Guidelines for use and Qualifying Criteria

Human normal immunoglobulin (Ig) is among the most expensive medicines in Sri Lanka, with a single course of 2g/kg for an average 60 kg adult costing approximately Rs. 1,250,000 per cycle. The state allocates 3.5%–4% of its total annual medicine expenditure, amounting to Rs. 1.5–2 billion, for procurement of Ig each year [1]. Despite its high cost, Ig is an essential, lifesaving treatment for certain medical conditions [2]. Therefore, judicious use of normal human immunoglobulin is imperative to contain healthcare cost and manage the limited resources available in the country.

This document outlines the guidelines for use and qualifying criteria for therapeutic and prophylactic use of human normal immunoglobulin. It is not intended to serve as a clinical practice guideline.

The indications and qualifying criteria listed below in the table (Table 1) are based on evidence-based guidelines and best practices, developed in consultation with relevant specialties [3, 4]. While this list is comprehensive, it is not exhaustive. Specialist clinicians are encouraged to restrict Ig prescriptions to the listed indications and criteria. However, the use of Ig beyond these criteria is permitted if the prescribing specialist provides a well-justified, evidence-based rationale for its use.

Preparations of Immunoglobulins and Uses

Human normal Ig is a sterile, purified preparation derived from pooled human plasma from thousands of donors [5]. Preparations of human normal Ig include:

- Normal immunoglobulin (containing 3%–12% protein) – for intravenous (IV) administration
- Normal immunoglobulin (containing 10%–18% protein) – for subcutaneous (SC) or intramuscular (IM) administration

The uses of human normal Ig can be categorized into three broad areas:

- Replacement therapy for primary and secondary immunodeficiencies
- Anti-inflammatory and immunomodulation for autoimmune and inflammatory diseases [6]

- Treatment or prevention of infections in specific clinical situations

Commercially available Ig preparations may vary in composition based on factors such as excipients (e.g., stabilizers), IgA content, and blood group antibodies [7]. Most Ig products are labelled for specific routes of administration (IV, SC, or IM), and these should be strictly followed. While some IVIg solutions can be administered subcutaneously, SC or IM formulations should not be given intravenously.

For immunomodulation in autoimmune and inflammatory diseases, intravenous route (IVIg) is the preferred route of administration. Both IVIg and SCIg are effective for immunodeficiency replacement therapy. SCIg offers advantages such as fewer systemic adverse effects, more stable serum IgG levels, improved quality of life, and cost-effectiveness compared to IVIg in these patients [8, 9]. The choice between IVIg and SCIg should be based on clinical indications, patient factors, preference and availability.

General Guidelines

1. Indications for human normal immunoglobulin

Routinely commissioned indications for Ig therapy fall under anti-inflammatory and immunomodulatory therapy and replacement therapy as detailed below. Clinicians may consider immunoglobulin for indications not listed in these guidelines if there is compelling, documented evidence of benefit. However, such decisions must be justified and based on established clinical rationale. Conditions in which Ig is not routinely commissioned are listed in Annexure 1.

It is recommended that outcome measures are monitored and documented in all patients whenever possible. Those on long-term therapy should be reviewed at regular intervals to identify lack of or inadequate response. If there is no or inadequate response, the prescribing clinician should consider alternative therapies and discontinue human normal immunoglobulin.

2. Prescription of human normal immunoglobulin

All prescriptions for Ig must be by a specialist of the relevant speciality or authorised by such a specialist. Prior approval of the Immunoglobulin Committee is

not required for initiation of therapy. However, if a patient requires long-term therapy exceeding one month, approval from the Immunoglobulin Committee is mandatory before continuation.

3. Request forms

A duly completed e-request form is mandatory when requesting Ig for a patient. All orders should be checked and verified by the issuing pharmacist to ensure compliance with this guideline. The forms are to be sent to the central Immunoglobulin Committee at the end of each calendar month by the chief pharmacist of each hospital.

4. Monitoring use

A central Committee appointed by the Ministry of Health, comprising specialists from all relevant specialities including immunology, haematology, rheumatology, neurology, nephrology, infectious diseases, paediatrics, dermatology, intensive care, cardiology, respiratory medicine, oncology and internal medicine along with representatives from the Medical Supplies Division will be responsible for the monitoring the use of, and authorisation of long-term treatment with Ig.

If any patient is expected to be on long term Ig therapy, exceeding one month, the prescribing specialist should seek approval from the Committee for continuation of therapy. This aims to promote rational use, support cost-effective prescribing, and enable centralized monitoring of Ig utilization

The Committee shall review all requests for Ig and grant prospective approval for continuation of long-term therapy. The Committee will also provide feedback to hospitals regarding their use, particularly if non-adherence to guidelines or if inappropriate use is identified.

5. Prioritisation of indications

When stocks are limited, priority will be given to indications marked in green, as well as any other conditions where the use of human normal Ig is considered lifesaving or strongly supported by high-level evidence, as determined by the Committee.

6. Dose calculation and vial dosing (for adults and children)

For individuals who are obese (Body mass index (BMI) over 27.5 kg/m²) or in patients with significant generalised oedema, human normal

immunoglobulin prescribing should be based on ideal body weight (IBW), except when used in the treatment of immunodeficiencies (replacement therapy or for treatment of infections). For all those with the BMI less than 27.5 kg/m², actual body weight (ABW) is to be used [10]. IBW based on booking weight or booking weight if non-obese should be used for pregnant patients.

Once the total dose required for the treatment course is calculated, the dose should be **rounded down** or **rounded up** to the nearest dose which can be administered **using whole vials** to minimise wastage. If less than 50% of a new vial is required to administer the calculated dose, the dose should be rounded down, and rounding up is acceptable if more than 50% of a new vial is required. However, to minimize the risk of underdosing or adverse effects due to excessive dosing, any rounding adjustment should be made without a marked deviation (less than 10%) from the originally calculated dose. (e.g. total calculated dose of 34 g, rounded up to 35 g if only 5g vials are available).

Part vials should never be used. Where the dose is split over multiple days, daily dose may differ to allow utilisation of whole vials.

For all patients with immune deficiencies including secondary immune deficiencies (for replacement therapy or for treatment of infections) **actual body weight** is to be used for dose calculation. The dose should be then **rounded up** to the nearest dose which can be administered **using whole vials** [11].

Example

An adult, height - 160 cm; ABW- 61 kg, BMI 23.8 kg/m² diagnosed with Guillain-Barre Syndrome meeting criteria for IVIg, is prescribed IVIg 2g/kg to be given over 5 days.

Total dose required:

2 g/kg X 61 kg: **122 g** (to be given over 5 days)

Number of 5g vials required:

122 g/5 g = **24.4 vials**

Rounded down to the nearest whole vial: **24 vials**

Split dose over 5 days:

Day 1 to Day 4 - 25 g / day (**5 vials / day**)

Day 5 - 20 g (**4 vials**)

**Table 1: Qualifying Criteria
Anti-inflammatory and immunomodulatory therapy**

	Code	Indication	Selection criteria	Alternative therapies and place of immunoglobulin	Recommended dosing
1.	A001	Allo-immune neonatal haemochromatosis or gestational allo-immune liver disease (GALD) (Acute treatment)	Decision to be made by consultant obstetrician in consultation with a gastroenterologist/hepatologist - Pregnant mothers with a previous adverse pregnancy outcome and clear post-mortem evidence of foetal haemochromatosis OR Women who have had an offspring with neonatal liver failure confirmed to be allo-immune neonatal haemochromatosis Affected neonates	There are no alternatives to Ig for those patients fulfilling eligibility criteria [12]	Maternal: IVIg at a dose of 1 g/kg (dose capped at 60 g per week) to at risk mothers at 14 weeks, 16 weeks and then weekly from 18 weeks' gestation until delivery between 37 and 38 weeks. Neonatal: Single dose of 1g/kg
2.	A002	Allo-immune thrombocytopenia (foetal-maternal/neonatal)	The diagnosis must be established by the relevant specialist.	Maternal: Ig is the primary treatment and sometimes combined with steroids.	Maternal: IVIg at a dose of 0.5g-1.0/kg/week - Low-risk obstetric history (no intracranial haemorrhage) from 20 weeks' gestation - In high-risk pregnancies, commence from as early as 12weeks' gestation. - If previous foetus or neonate has had intracranial haemorrhage After 28 weeks - dose 1g/kg/week Before 28 weeks- dose 2g/kg/week Neonate

				<p>- Single dose of 1g/kg</p> <p>- If thrombocytopenia persists, 2nd dose of 1g/kg is given</p>
			<p>Neonate:</p> <p>First line treatment is platelet transfusion</p> <p>IVIg is second line treatment [13]</p>	
3.	A003 ANCA-associated systemic vasculitis (AAV)	Refractory/relapsing AAV AND conventional immunosuppressive therapy is contra- indicated e.g. presence of severe infection OR in pregnancy as bridging therapy	<p>For new-onset or relapsing ANCA vasculitis, with organ-threatening or life-threatening disease, a combination of glucocorticoids and either rituximab (preferred for relapsing disease) or cyclophosphamide first line.</p> <p>For non-organ-threatening or non-life-threatening disease a combination of glucocorticoids and rituximab, methotrexate or mycophenolate mofetil is recommended [14].</p> <p>IVIg is primarily used as an adjunctive therapy. In rare cases, as a sole treatment if conventional immunosuppressive therapy is contra-indicated.</p>	IVIg at a dose of 2 g/kg over 2 to 5 days in divided doses, repeat dosing determined by a specialist based on clinical response and indication.
4.	A004 Autoimmune encephalitis (Acute treatment)	Diagnosis established by a neurologist, or in consultation with a neurologist* AND	<p>Steroids are the 1st line, with or without plasma exchange.</p> <p>Rituximab has been shown to be effective in anti-NMDA</p>	<p>IVIg at a dose of 2 g/kg over 2 to 5 days in divided doses initially.</p> <p>Repeated at 3 - 6 weeks or longer intervals, and repeat course up to 3 times if</p>

			Functional disability caused by seizures, encephalopathy, stiffness, cognitive dysfunction or other relevant neurological sequelae <i>*Patients with suspected Anti-NMDA receptor autoimmune encephalitis or other forms of autoimmune encephalitis should ideally be managed under the care of a neurologist. If direct neurologist care is not feasible, an early opinion should be obtained to guide the diagnostic workup and treatment plan.</i>	receptor autoimmune encephalitis and should be considered early in the treatment course. IVIg may be necessary where long- term oral immunosuppression is ineffective or contra-indicated [15].	necessary, as determined by a specialist based on clinical response and indication.
5.	A005	Autoimmune haemolytic anaemia (AHA, including Evans syndrome) (Acute treatment)	Symptomatic or severe anaemia AND Refractory to conventional treatment with corticosteroids, OR Corticosteroids contra-indicated, OR As a temporising measure prior to splenectomy	The place of IVIg in AHA is limited. It is reserved for patients unresponsive to steroids and rituximab or where steroids are contra- indicated as a rescue measure [16, 17]	IVIg at a dose of 1-2g/kg over 2 to 5 days in divided doses. May repeat on relapse as determined by a specialist based on clinical response and indication.
6.	A006	Catastrophic antiphospholipid syndrome (CAPS) (Acute treatment)	Diagnosis of definite or probable CAPS by a specialist team including a rheumatologist or a haematologist AND Has severe thrombocytopenia AND PLEX is either unavailable or contra-indicated OR if there is deterioration following PLEX	Optimal therapy include combination of corticosteroids, anti-coagulants and plasma exchange (PLEX) or IVIg [18].	IVIg at a dose of 2g/kg over 4 to 5 days in divided doses.

7.	A007	Guillain-Barre Syndrome (GBS) (Acute treatment)	Diagnosis of GBS (or variant) by a specialist neurologist or a physician or paediatrician in consultation with a neurologist AND Significant disability (Hughes Grade 3 or more) OR Disease progression towards intubation and ventilation OR Poor prognosis	Plasma exchange is equally effective as IVIg in GBS [19].	2 g/kg as early as possible after the diagnosis is confirmed, administered over 5 days. Second or additional doses of IVIg are not effective in the treatment of GBS and may be associated with potential harm [20]. Patients with mild symptoms and/or non-progressive disease and those not requiring intubation do not require IVIg [21].
8.	A008	Haemolytic disease of newborn (HDN) (Acute treatment)	- Adjunct to continuous multiple phototherapy in cases of Rhesus haemolytic disease, or ABO haemolytic disease For Rising serum bilirubin by more than 8.5 micromol/litre per hour despite intensive phototherapy	Adjunct to phototherapy [22].	Single dose of IVIg - 0.5g/kg over 4 hrs
9.	A009	Haemophagocytic Lymphohistiocytosis (HLH) (Acute treatment)	Diagnosed by a specialist panel including a specialist haematologist or a rheumatologist.	First line therapy includes high dose corticosteroids, and IL-1 receptor inhibition (Anakinra, which is currently unavailable in Sri Lanka) if steroid refractory. IVIg may be considered along with corticosteroids particularly if there is cardiac or CNS involvement. Other therapies including etoposide and cyclosporin [23, 24].	IVIg at a dose of 1g/kg for 2 days or 0.4g/kg for 5 days.
10.	A010	Immune thrombocytopenia (Acute treatment)	Immunoglobulin is used only in four situations: - Life-threatening bleeding where an immediate increase in platelet count is required	Primary treatment modalities are corticosteroids, thrombopoietin receptor agonist, rituximab and splenectomy [25].	Adults IVIg 1g/kg as a single dose.

		<ul style="list-style-type: none"> - Where the patient is refractory to all other treatment to maintain the platelet count at a level to prevent haemorrhage. It may need to be given every 2-3 weeks during a period where other second line treatments are being tried. - Moderately severe bleeding in a patient at higher risk of subsequent severe bleed. <p>Patients with mucosal bleeding or bleeding from multiple sites or a previous history of severe bleeding and are at higher risk of a subsequent severe bleed</p>	<p>IVIg is used only when a more rapid rise in platelets are required, and this effect lasts for only 1-2 weeks [26].</p>	<p>A 2nd dose may be required after 24 – 48h ours, if severe or life-threatening bleeding or if a haemostatically adequate platelet count is not achieved.</p> <p>The 2nd dose (1g/kg) may be considered at day 5 to 7</p> <p><u>Children</u></p> <p>IVIg 0.8 – 1.0 g/kg as a single infusion.</p> <p>A 2nd dose may be required after 24 – 48 hours, if it is a severe or life-threatening bleeding or if a haemostatically adequate platelet count is not achieved. The 2nd dose (1g/kg) may be considered at day 5 to 7.</p>	
11.	A011	Immunobullous diseases (Acute treatment)	<p>Severely affected AND Corticosteroid treatment with adjuvant immunosuppressive agents has failed or is inappropriate</p>	<p>IVIg is reserved for patients who are refractory to conventional corticosteroid therapy in acute settings [27].</p>	<p>IVIg at a dose of 1 - 2 g/kg over 2–5 days in divided doses.</p>
12.	A012	Inflammatory Myopathies Dermatomyositis (DM) Polymyositis (PM) Or any other inflammatory myositis	<p>Diagnosis of myositis by a neurologist or rheumatologist or dermatologist AND Has significant muscle weakness OR DM with refractory skin involvement.</p>	<p>First line of treatment is high dose steroids with CsDMARDs (Methotrexate, azathioprine, tacrolimus, ciclosporin, and mycophenolate mofetil) Second line rituximab and cyclophosphamide should be considered. IVIg is indicated for DM/PM refractory to corticosteroids and CsDMARDs, used in</p>	<p>IVIg at a dose of 2g/kg given over 2 to 5 days and may be repeated after 6 weeks or at longer intervals as determined by a specialist based on clinical response and indication.</p>

13.	A013 Kawasaki disease (Acute treatment)	Clinical diagnosis of Kawasaki disease made by a paediatrician	combination with other immunosuppressant therapy [28] IVIg in combination with anti-inflammatory doses of aspirin is the treatment of choice [29]	IVIg 2 g/kg single dose. A second dose may be given if no response, or if relapse within 48 hrs
14.	A014 Multifocal motor neuropathy (MMN) (Long term therapy)	Diagnosis by a neurologist AND Significant functional impairment inhibiting normal daily activities	IVIg is the primary treatment modality. There are no alternative treatments at present [30].	IVIg at a dose of 2 g/kg given over 2 - 5 days in divided doses and repeated after 6 weeks or at longer intervals as determined by a specialist based on clinical response and indication. These patients should be managed under the care of a neurologist and closely monitored. If no significant, measurable, and functionally meaningful improvement is observed after three doses, IVIg should be discontinued .
15.	A015 Myasthenia Gravis (MG) including Lambert-Eaton Myasthenic Syndrome (LEMS) (Acute and long-term use)	Diagnosis of MG or LEMS by a neurologist or a in consultation with a neurologist AND Acute exacerbation (myasthenic crisis) OR Weakness requires hospital admission OR Prior to surgery and/or thymectomy	IVIg is reserved for patients unresponsive or refractory to other treatment including plasma exchange, steroids and immunosuppression (e.g. azathioprine, mycophenolate, rituximab) [31, 32]	IVIg at a dose of 1-2g/kg in over 2 – 5 days in divided doses.

16.	A016	Paediatric inflammatory multisystem syndrome temporarily associated to COVID-19 (PIMS-TS) (Acute treatment)	Clinical diagnosis of PIMS-TS by a paediatrician, paediatric consultant in infections or paediatric immunologist	Consider corticosteroids as first-line therapy while reserving IVIg for those where there is difficulty in distinguishing Kawasaki disease from MIS-C.	IVIg single dose of 2 g/kg single dose with high-dose aspirin A second dose may be given if no response, or if relapse within 48 hrs
17.	A017	Post-transfusion hyperhaemolysis (Acute treatment)	Treatment of acute post-transfusion hyperhaemolysis	In combination with IV methylprednisolone – Ig is given as a first line therapy	1g/kg for 2 days given with IV methylprednisolone
18.	A018	Post-transfusion purpura (Acute treatment)	Sudden severe thrombocytopenia 5 to 10 days post-transfusion of blood products, AND Active bleeding	This is now rare due to the use of leucocyte- reduction of blood components	IVIg 1-2g/kg in divided doses over 2 – 5 days
19.	A019	Rapidly progressive myelitis (Transverse myelitis) (Acute treatment)	Diagnosis of rapidly progressive myelitis (Transverse myelitis) by a neurologist or in consultation with a neurologist When not responding to IV methylprednisolone (5 – 7 g or equivalent in children) and plasma exchange. Or when plasma exchange is not available or delayed or contraindicated, Ig can be used before plasma exchange AND Significant functional impairment	IV methylprednisolone OR plasma exchange are first line therapies for transverse myelitis.	IVIg at a dose of 2 g/kg over 2 - 5 days in divided doses.
20.	A020	Refractory Chronic Inflammatory Demyelinating	Diagnosis of CIDP by a neurologist or a in consultation with a neurologist AND	IVIg is generally not considered 1 st line treatment, unless corticosteroids are contra-	IVIg at a dose of 2 g/kg given over 2 - 5 days in divided doses.

		<p>Polynuropathy (CIDP) (Long term therapy)</p>	<p>Significant functional impairment inhibiting normal daily activities AND if corticosteroids are contraindicated or plasma exchange is contraindicated or unavailable and patient is refractory to other immunosuppressants e.g. (azathioprine, mycophenolate, rituximab).</p>	<p>indicated and plasma exchange is not available. May be preferable in patients with motor predominant CIDP.</p>	<p>Repeated after 6 weeks or at longer intervals as determined by a specialist based on clinical response and indication. Patients should be managed under the care of a neurologist and closely monitored. Long-term IVIg therapy should be considered only for those who demonstrate meaningful functional improvement during the induction phase. An annual clinical review should be conducted to determine the need for ongoing IVIg treatment [33].</p>
21.	A021	<p>Refractory Neuromyelitis Optica (NMO), Myelin Oligodendrocyte Glycoprotein Associated Disorders (MOGAD) (Long term therapy)</p>	<p>Diagnosis established by a neurologist AND Refractory to at least two treatments, including steroids and an immunosuppressant (any of mycophenolate mofetil/ rituximab/ azathioprine/ methotrexate)</p>	<p>IVIg is to be considered if two first line therapies have failed. Rituximab is an effective treatment for prevention of relapses in Neuromyelitis Optica Spectrum Disorder (NMOSD) and should be considered early in the course for those with severe or refractory symptoms [34]. The efficacy of rituximab in myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is less clear. Importantly, approximately 50% of MOGAD patients have a monophasic course, and do not require long-term immunosuppression [35].</p>	<p>IVIg 1g/kg daily over 2 days then 1g/kg monthly for first year Titrated to 2g/kg if relapses occur despite on-going therapy at 1g/kg as determined by a specialist based on clinical response and indication.</p>

Replacement therapy (inborn errors of immunity and secondary immunodeficiency)

	Code	Indication	Selection criteria	Alternative therapies and place of immunoglobulin	Recommended dosing
22.	R001	Inborn error of immunity (IEI) associated with significant antibody deficiency (excluding specific antibody deficiency) – long term use	A specific IEI diagnosis requiring immunoglobulin therapy must be established by a specialist team including an immunologist.	Ig is the only definitive treatment for antibody deficiency [36, 37].	Initiate at 0.4–0.6 g/kg, 3 to 4 weekly. Dose requirements may increase and should be based on clinical outcome and trough IgG levels [38].
23.	R002	HSCT in IEI – long term use	IEI patients undergoing HSCT	Ig is the only definitive treatment for antibody deficiency (38).	Initiate at 0.4–0.6 g/kg/month. Dosing requirements may increase and should be based on clinical outcome. Because of the possibility of B-cell reconstitution, evaluation of immune function (off Ig) is required at 2 years
24.	R003	Secondary immunodeficiency * – long term use	<ul style="list-style-type: none"> – Recurrent or severe bacterial infection AND EITHER <ul style="list-style-type: none"> – Serum IgG level of <4 g/l OR <ul style="list-style-type: none"> – Proven specific antibody failure defined as failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines. 	Ig is reserved for those patients in whom prolonged antibiotic prophylaxis proves to be ineffective for protection from bacterial infections. Many patients will achieve protection from infections with prolonged antibiotic prophylaxis [39].	Initiate trial at 0.4–0.6 g/kg/month for a period of 6 to 12 months. Long-term maintenance treatment should be based on clear evidence of benefit from this trial and require panel approval. Dose requirements may increase and should be based on clinical outcome
25.	R004	Specific antibody deficiency – long term use	<ul style="list-style-type: none"> - Diagnosis by a clinical immunologist - Severe, persistent, or recurrent bacterial infections despite continuous oral antibiotic therapy for 6 months AND	Ig is reserved for those patients in whom prolonged antibiotic prophylaxis proves to be ineffective for protection from bacterial infections [37, 40].	Initiate trial at 0.4–0.6 g/kg/month for a period of 6 to 12 months. Long-term maintenance treatment should be based on clear evidence of benefit from this trial and require panel approval.

		<ul style="list-style-type: none"> - Documented failure of serum antibody responses to unconjugated pneumococcal or other polysaccharide vaccine challenge 	Dose requirements may increase and should be based on clinical outcome
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*Secondary antibody deficiency refers to hypogammaglobulinaemia resulting from B-cell malignancies (such as CLL, NHL, MM, or other relevant disorders confirmed by a haematologist), following haematopoietic stem cell transplantation, or secondary to treatment with medicines including monoclonal antibodies targeting B cells or plasma cells (e.g. rituximab, daratumumab) and related therapies.

Treatment and prophylaxis of infections

The decision to treat with human normal immunoglobulin for the following indications should **always** be in concurrence with a microbiologist or a virologist.

Code	Indication	Selection criteria	Position of immunoglobulin and alternative therapies	Recommended dosing
1. I001	Acquired red cell aplasia associated with chronic parvovirus B19 infection (Acute treatment)	Parvovirus B19 infection confirmed by PCR AND Evidence of high viral load	Transient aplastic crisis due to acute parvovirus infection requires urgent transfusion rather than IVIg. In acquired red cell aplasia due to chronic infection, Ig is an adjunct to transfusion.	IVIg at a dose of 1-2g/kg over 2 to 5 days divided doses. This may be repeated on relapse and for a 2 nd relapse.
2. I002	Hepatitis A	Ig is recommended in addition to hepatitis A vaccine for contacts of hepatitis A who are less able to respond to vaccine <ul style="list-style-type: none"> - Age 60 years or over OR - those with immunosuppression and those with a CD4 count <200 cell per microlitre, OR - those at risk of severe complications (those with chronic liver disease including chronic hepatitis B or C infection) 	Vaccine should be administered within 2 weeks of exposure	Intramuscular normal human immunoglobulin (10%-18%) <ul style="list-style-type: none"> <10 years 500mg >10 years 1000mg

3.	I003	Measles	<p>Those who have had a significant exposure</p> <p>AND</p> <ul style="list-style-type: none"> - Immunosuppressed patients who are known to be susceptible - Pregnant women identified as susceptible based on vaccine history and /or antibody testing - Infants under 9 months of age 	<p>For immunosuppressed contacts, pregnant women and infants less than 6 months of age, Ig is mainstay management.</p> <p>MMR vaccine may be offered to infants between 6 to 8 months of age, ideally within 72 hours.</p>	<ul style="list-style-type: none"> - Immunosuppressed patients – 0.15 g/kg of IVIg within 72 hours of exposure. It can be given up to 6 days. - For pregnant contacts, approximately 3000mg of human normal Ig - Infants 0.6 ml/kg up to a maximum of 1000mg of HNIG
4.	I004	Polio	<p>To prevent or attenuate an attack:</p> <p>An immunocompromised person inadvertently given live polio vaccine,</p> <p>OR</p> <p>An immunocompromised person whose contacts are inadvertently given live polio vaccine</p>	<p>IVIg is the first line treatment</p>	<p><1 year: 250mg</p> <p>1 – 2 years: 500mg</p> <p>>3 years: 750mg</p> <p>If poliovirus is grown in stool sample, repeat Ig at 3 weeks.</p> <p>Continue weekly stool collection and administration of Ig 3- weekly until stool is negative for poliovirus on two occasions</p>
5.	I005	Severe or recurrent Clostridium difficile infection (CDI) colitis	<p>- short term use</p>	<p>For fulminant or recurrent CDI unresponsive to appropriate antibiotics.</p>	<p>0.4 g/kg, one dose, and consider repeating once</p>
6.	I006	Staphylococcal (including PVL- associated sepsis) or streptococcal toxic shock syndrome (TSS)	<p>- short term use</p>	<p>IVIg is reserved for patients with life-threatening disease who fail to achieve rapid improvement with antibiotic therapy, however the evidence is controversial.</p>	<p>Early administration - 1g/kg single dose</p> <p>If refractory/ or no improvement in 24 hours, a further 2g/kg single dose may be repeated</p>

		therapy and other supportive measures AND - Life-threatening		
7.	I007	Suspected tetanus case	Person with clinical symptoms suggestive of localised or generalised tetanus/ suspected case of tetanus	In the absence of IV Tetanus Immunoglobulin, IV Ig is the recommended, in addition to wound debridement, antimicrobials, and supportive care
8.	I008	Varicella zoster	Significant exposure to chickenpox (varicella) or shingles (zoster) during the infectious period AND At increased risk of severe chickenpox i.e. immunosuppressed individuals, neonates and pregnant women AND No antibodies to varicella-zoster virus (based on VZV antibody testing)	0.2 g/kg of IVIg (i.e. 4 ml/kg for a 5 % solution) Ideally within 7 days of exposure, and can be offered up to 14 days.
9.	I009	Selected cases of severe viral infections associated with immunodeficiency	These include - viral pneumonitis due to varicella zoster virus (VZV), respiratory syncytial virus (RSV), cytomegalovirus (CMV), human parainfluenza virus (HPIV) in immunocompromised patients including post-transplantation (H SCT and solid organ) - persistent aplastic anaemia due to parvovirus B19 among immunocompromised patients	IVIg should be administered at a dose of 1 – 2 g/kg over 2 to 5 days in divided doses

		<ul style="list-style-type: none"> - encephalitis due to enteroviruses in immunocompromised patients - In post-HSCT patients, viral reactivations such as CMV or Parvovirus with high viral loads or resistance to primary therapy 		
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Note:

Human normal immunoglobulin is not routinely recommended for neonatal sepsis or sepsis in intensive care units not related to specific toxins or C. difficile.

The decision to use human normal immunoglobulin should be made in concurrence with a microbiologist.

In addition to the indications listed above, human normal immunoglobulin may be prescribed for any other indication based on current evidence and judgement of a Medical Virologist/Microbiologist.

ANNEXURE 1

Indications in which Human Normal Immunoglobulin is NOT routinely commissioned

1. Acquired red cell aplasia or Aplastic anaemia other than due to parvovirus B19
2. Adrenoleukodystrophy
3. Alzheimer's disease
4. Amyotrophic lateral sclerosis
5. Atopic dermatitis/eczema
6. Autoimmune neutropenia
7. Autologous BMT
8. Cerebral infarction with antiphospholipid antibodies
9. Chronic facial pain
10. Chronic fatigue syndrome
11. Chronic immune thrombocytopenia (ITP)
12. CNS vasculitis
13. Critical illness neuropathy
14. Graves' ophthalmopathy
15. Haemolytic uraemic syndrome
16. Immunodeficiency secondary to paediatric HIV infection
17. Inclusion body myositis
18. Intractable childhood epilepsy
19. Multiple sclerosis
20. Neonatal sepsis (prevention or treatment)
21. Opsoclonus-myoclonus syndrome - adult carcinoma related
22. Paediatric Acute-onset Neuropsychiatric Syndrome (PANS)/ Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS)
23. Paediatric myocarditis
24. Paraneoplastic syndromes not known to be T or B cell mediated
25. POEMS (polyneuropathy organomegaly, endocrinopathy/oedema, monoclonal protein, skin changes)
26. Pyoderma gangrenosum
27. Sepsis in the intensive care unit not related to specific toxins *Clostridium difficile*
28. SLE with secondary immunocytopenias
29. Systemic juvenile idiopathic arthritis
30. Toxic epidermal necrolysis, including Steven Johnson Syndrome

Normal Human Immunoglobulin - National Guidelines for Use and Qualifying Criteria

These guidelines were developed by a committee comprising specialists from relevant specialties. The recommendations are based on existing commissioning criteria from international authorities, as well as evidence-based clinical practice guidelines and published literature. The recommendations were adapted to the Sri Lankan context, considering the local disease burden, patterns of use, availability of alternative treatments, and resource constraints within the Sri Lankan healthcare system. Input from relevant specialties and clinicians was incorporated to ensure clinical relevance, feasibility, and cost-effective use of immunoglobulin across state healthcare institutions.

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Professor Colvin Goonertne – An Appreciation

On behalf of the Editorial Board of the Sri Lanka Prescriber (SLP) I am writing this brief note to acknowledge the services of Professor Colvin Gooneratne to the SLP.

Professor Colvin Gooneratne served in the Editorial Board of the SLP for a continuous period of 31 years (1993 to 2024). He had been a Co-Editor previously for brief periods also in the 1980s for the previous pocket version of the bulletin, The Prescriber.

It was Professor Senaka Bibile, who way back in the 1950s recognized the need for continuous updating of the medical profession and the public about rational prescribing and correct use of medicines. Towards educating the medical profession he single handedly wrote the Ceylon Hospitals Formulary in 1959. As a continuous medical education exercise he started the drug information journal, Formulary Notes first published in 1966. In the latter half of the 20th century, when updated information on medicines came from textbooks and journals, the Formulary Notes and its follower, The Prescriber, was a much sought after source of practical therapeutic information for the doctors and medical students.

In order to honour Professor Bibile and to continue the task of educating the prescribers, the Department of Pharmacology of the Colombo Medical Faculty took it upon itself to continue to publish the Prescriber journal. After Professor Bibile, the work of the Prescriber was mostly handled by Professor NDW Lionel, with help from departmental colleagues and the extended faculty. When Professor Lionel died in 1982 his void was never filled. The Department of Pharmacology experienced an acute shortage of staff and for various other reasons the Prescriber suffered. The Journal issues were put out in a haphazard manner and there were years during which its publication ceased.

It was during this period that publication of the Prescriber was reactivated by Professor Colvin Gooneratne, along with the then Professor of Pharmacology, Professor Tilak Weerasinghe. Since he joined the Editorial Board he arranged for regular meetings of the Board, which he chaired. He wrote to identified authors and took great pains to canvass articles. Slowly he was able to get a regular supply of articles enabling timely publication. Instructions to authors were developed by Professor Goonarathne and the SLP took the shape of a regular medical journal.

Professor Colvin was very particular about the presentation of the articles in the SLP. He personally

edited all the articles on aspects such as language, syntax, brevity so that the message conveyed to the reader was clear. During this exercise he had to interact with the authors of the articles and some of these interactions were not very cordial. Yet, Professor Colvin persisted in seeing that what was published in the SLP met editorial standards. The Journal also went through changes in its name, format and size during this period and these changes were supervised by him. Once the journal was in regular publication he delegated some of the work to his colleagues.

During the period that Prof Colvin was in the Editorial Board the SLP got membership of the International Society of Drug Bulletins (ISDB). Membership of this Society is given on strict criteria about editorial independence from the pharma industry.

The present Editorial Board of the SLP appreciates the commitment and dedication shown by Professor Colvin Goonertne for the sustenance of the journal and thank him for all his work.

Professor R. L. Jayakody

Co-editor, Editorial Board of Sri Lanka Prescriber

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