Summer Training at
**PlasmaGen Biosciences, Bengaluru**
*(April 1, 2019- June 1, 2019)*

# REPORT

# *Therapeutic and price benefits of multiple intravenous immunoglobulins strengths (10g/100ml, 5g/100ml, 2.5g/50ml) & Excipients*


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Under the guidance of

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**MBA in Pharmaceutical Sciences**
**2018-2020**




Institute of Health Management and Research
Jaipur

2019

INSTITUTE OF HEALTH
MANAGEMENT RESEARCH
(WHO Collaborating Centre for District Health System Based on Primary Health Care)

IIHMR UNIVERSITY

## CERTIFICATE

This is to certify that **Manreet Kaur** has undergone Summer Training at **PlasmaGen Biosciences** from 1st April 2019 to 1st June 2019.

The candidate herself has completed the project assigned to her in the summer training. Her approach to project was sincere and proactive. This Summer Training is in partial fulfillment of the course requirement recommended for the award of MBA in Pharmaceutical Management.

I wish her success in all her future endeavors.

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# CERTIFICATE OF INTERNSHIP

THIS CERTIFICATE IS PRESENTED TO

*Ms. Manreet Kaur*

In recognition to the valuable contribution towards the Marketing Research Project
in the field of Blood Plasma Products
on the topic

**"THERAPEUTIC AND PRICE BENEFITS OF MULTIPLE IVIG STRENGTHS & EXCIPIENTS AND USE OF SOCIAL MEDIA TO INCREASE BRAND RECALL"**

April, 2019 - May, 2019

**Dr. Ranjeet S. Ajmani**
Chief Executive Officer

PlasmaGen Biosciences

# ACKNOWLEDGEMENT

*The project undertaken for summer internship was successfully completed with help and guardianships of some conversant persons without whom this would have been immaterial in its approach.*

*I am extremely privileged to have got this all along the completion of my project. All I have done owes sincere thanks to my mentor for this project Mr. Sandeep Narula, Dean Academics Affair, Assistant Professor, IIHMR University. His keen interest and guidance till the completion of this project was indispensable.*

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*It is worth appreciating efforts of encouraging reflection from Ms.Aarthi Gunnan Rajkumar, Senior Manager, HR and Admin at PlasmaGen Biosciences. My gratitude lies towards IT, admin and smiling staff of this company whom I cannot show my gratitude just in terms of words.*
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*Manreet Kaur*
*Student*
*School of Pharmaceutical Sciences*
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# ABBREVATIONS

| | |
|---|---|
| IVIg | Intravenous immunoglobulin |
| SAARC | South Asian Association for Regional Cooperation |
| GBS | Guillain Barre Syndrome |
| HIV | Human Immunodeficiency Virus |
| KD | Kawasaki Disease |
| ITP | Immune thrombocytopenic Purpura |
| ADEM | Acute disseminated Encephalomyelitis |
| XLA | X-linked Agammaglobulinemia |
| CVID | Common Variable Immunodeficiency |
| HIGM | Hyper IgM Syndrome |
| WAS | Wiskott Aldrich Syndrome |
| CLL | Chronic Lymphocytic Leukemia |
| Paed | Paediatrics |
| Rheumat | Rheumatology |
| Neuro | Neurology |
| Int.Med | Internal Medicine |
| Hemat | Hematology |
| Nephro | Nephrology |
| NAT | Neonatal Alloimmune Thrombocytopenia |
| CIDP | Chronic Inflammatory Demyelinating Polyneuropathy |
| MMN | Multifocal Motor Neuropathy |
| M.Crisis | Myasthenia Crisis |
| CVID | Common Variable Immunodeficiency |
| PID | Primary Immunodeficiency |
| IgA | Immunoglobulin A |
| SLE | Systemic Lupus Erythematosus |
| R. epilepsy | Refractory epilepsy |
| PLEX | Plasmapheresis |
| A. Dermatitis | Atopic Dermatitis |

# Profile of the Organization

**PlasmaGen Biosciences**, headquartered in Bengaluru, a biopharmaceutical company specialized exclusively in *Plasma Protein Therapy* works for an endeavor to provide safe plasma products in India and SAARC region. It has leveraged the growth of this industry by conceptualizing and formulating various plasma policies and hemovigilance programs with the government of India.

With in depth domain of plasma protein therapeutics it tip-toed in the industry on September, 2007. Adhering to its brand promise of being committed to life it caters the requisites of diverse realms as hematology, oncology, neurology, pediatrics, immunology, rheumatology and dermatology. It has shown its continued conviction in the domestic pharmaceutical market by offering widest range of plasma products in India, which include:

| Name of Product | Composition | Strength |
|---|---|---|
| PlasmaGlob | Intravenous Immunoglobulin | 2.5g/50ml, 5g/100ml |
| AlbuMax | Albumin | 20% in 100ml |
| PlasmaRho D I.V. | Rho (D) Immune Globulin | 300 μg/2ml |
| PlasmaRho-I.M. | Rho (D) Immune Globulin | 300 μg/2ml |
| PlasmaRAB | Human Rabies Immunoglobulin | 300 I.U./2ml |
| PlasmaHep | Hepatitis-B Immunoglobulin | 100 I.U/ml & 200 I.U/2ml |
| VerBumin | Albumin | 20% in 100ml |
| Gammafact-VIII | Factor VIII | - |

*Table 1: Plasma Products of PlasmaGen Biosciences*

Working to transform rare lives, of which diagnosis is a serious shortfall, it aims consistently in empowering knowledge through various conferences and symposiums.
In 2007, it has raised ~$25 million in a round led by 'Eight Roads Venture India' with participation from US- based F-Prime capital partners (YS, 2017).

The top competitors of the company are Reliance life sciences presided by Mr. K.V. Subramaniam and Intas owned by Mr. Nimish Hasmukhbhai Chudgar.

(PlasmaGen Biosciences)

# Introduction

Intravenous IgG (IVIg) is a blood product derived from pooled plasma, comprising of polyclonal immunoglobulin G (IgG). It is employed not only in immunodeficiency disorders but also in immune mediated disorders (Gilardin, Bayry, & Kaveri, 2015).

Depending on the concentration of IVIg it can exercises both pro-and anti-inflammatory activities. The potential working mechanism for immunomodulatory effect of IVIg can be dependent either on Fc or Fab part of IgG molecule (Nagelkerke & Kujipers, 2015). Upon administration at low dose, complement activation or binding of Fc fragment of IgG to IgG-specific receptors occurs on the immune effector cells. The high dose of IVIg acts as anti-inflammatory in nature (Durandy, et al., 2009).

The US-FDA approved indications for IVIg include :

1. Primary Immunodeficiency (PIs)
2. Prevention of bacterial infections in hypogammaglobulinemia and recurrent bacterial infections due to B-cell chronic lymphocytic leukemia (CLL)
3. Prevention of coronary artery aneurysm associated with Kawasaki Disease (KD)
4. Decrease the risk of septicemia and other acute graft-versus-host disease (GVHD) subsequent of bone marrow transplantation
5. Reduction of severe bacterial infections in pediatric patients infected with HIV
6. Rapid rise in platelet count in idiopathic thrombocytopenic purpura
7. Management of polyneuropathies such as Guillain-Barre Syndrome (GBS), chronic inflammatory demyelinating polyneuropathy
8. Maintenance therapy in multi focal motor neuropathy (Perez, et al., 2017)

IVIg is used off label for growing number of off label indications in various specialties of neurology, pediatrics, rheumatology, internal medicine, intensivists, hematology, oncology, nephrology and dermatology. Being a blood derived product its cost is relatively higher because of safety and manufacturing processes, and also plasma donation being not allowed in India, there is further upsurge in its cost.

A higher concentration of IgA and anti-Rh blood group, D antigen exacerbate the adverse effects associated with infusion of IVIg. The adverse effects associated with IVIg as reported in literature are as (1) mild- light headache, fever, chills and fatigue (2) moderate- chest pain, anhelation, vomiting, severe headache (3) severe- hypertension, anaphylaxis, bronchospasm, and altered consciousness (Guo, Tian, Wang, & Xiao, 2018). With careful screening of the patients prior to treatment, premedication's with antihistamines and analgesics, and adjustment of infusion rate, the side effects can be controlled to a greater extent (Jolles, Sewell, & Misabh, 2005).

Usage of organic osmolytes as stabilizers is employed in the IVIg products to prevent aggregation of IgG molecules during its manufacturing and storage. These are sugars- such as sucrose, glucose and maltose, polyols- sorbitol and amino acids- glycine and L-proline. The profile of these molecules differ on their effect on blood glucose and renal function, and so does their risk profile in regard to serious adverse events (Ochs & Siegel, 2010).

| Neurology | Pediatrics | Hematology | Immunology | Dermatology | Nephrology, rheumatology, ophthalmology and others |
|---|---|---|---|---|---|
| Guillain Barre syndrome | Kawasaki disease | Immune thrombocytopenia | Primary antibody deficiencies (XLA,CVID, HIGM, WAS) | Dermatomyositis | Vasculitis |
| Multifocal motor neuropathy | Septicemia | Post bone marrow transplant | Secondary antibody deficiencies (myeloma, CLL, drugs and other causes) | Toxic epidermal necrolysis | Systemic lupus erythematosus |
| Chronic inflammatory demyelinating polyneuropathy | Rh incompatibility | Myeloma and chronic lymphocytic leukemia | - | Blistering diseases | Streptococcal toxic shock syndrome |
| Dermatomyositis and inflammatory myopathies | - | Parvovirus B19-associated aplasia | - | Immune urticaria | Birdshot retinochoroidopathy |
| Myasthenia crisis Lambert-Eaton syndrome | - | Immune neutropenia | - | Atopic dermatitis | Autoimmune uveitis |
| Stiff person syndrome | - | Immune hemolytic anemia | - | Scleromyxodema | Mucous membrane pemphigoid |
| - | - | HIV associated thrombocytopenia | - | - | - |
| - | - | Neonatal alloimmune Thrombocytopenia | - | - | - |

*Table 2: Section wise usage of IVIg in various indications of different specialties*

IVIg is usually employed as immunology replacement therapy at dosage of 0.4g/kg while in others it is usually used as 2g/kg. The list is not exhaustive, aim solely being to cover major indications under various specialties.
Modified from (Jolles, Sewell, & Misabh, 2005).

# RATIONALE

Intravenous immunoglobulins finds its usage in various indications and remain the first line therapy for handful of them. Being an human derived product, its cost is on the higher verge which is not economical for all the patients needing immunoglobulins.

There are different strengths of intravenous immunoglobulin available in the market, of which 10g/100ml is fetching pens of various physicians since its cost is lesser than two vials of 5g/100ml. The best suited alternative of this product is plasmapheresis that shows similar efficacy, and is preferred over the former for its cost issues.

With increasing burden of rare diseases and the growing plasma market with expected CAGR of 10.54% (2015-2020), company needs to work in the segments of its competitors and work heftily on affordability concerns.

# OBJECTIVES

To assess therapeutic and price benefits of multiple intravenous immunoglobulin strengths (10g/100ml, 5g/100ml, 2.5g/50ml).

a. To evaluate disease indications and frequency usage pattern of different strengths of IVIg in different specialties of various cities
b. To categorize substitute preference over IVIg
c. To know the usage pattern of various strengths of IVIg in different specialties of various cities
d. To comprehend the segmenting of IVIg in various segments of being curative, supportive or replacement therapy
e. To understand the side effects being encountered with administration of IVIg, and its treatment thereafter
f. To know the perception of doctors regarding excipients present in IVIg
g. To know which specialty has maximum usage of IVIg
h. To find out the minimum inventory maintained in hospitals for IVIg
i. To find out the decision making authority for IVIg in hospitals

# RESEARCH METHODOLOGY

❖ ***Area of study***

- Tier 1 cities: Mumbai, Bengaluru, NCR
- Tier 2 cities: Jaipur, Trivandrum, Cochin

❖ ***Research Design***

Descriptive study was planned, with focused and detailed questionnaire that had been carefully analyzed and articulated at the outset.

❖ ***Sampling***

- Both private and government hospitals were targeted
- Different specialties were targeted to have diverse data- neurology, paediatrics, dermatology, rheumatology, intensivist, internal medicine, hematology

❖ ***Data collection***

**Tools**

- Structured questionnaire was designed for doctors and purchase managers which was used as reference.

**Techniques**

- Face to face interviews were employed as survey techniques

❖ ***Data Analysis***

MS-Excel was employed for analyzing the data.

## RESULTS AND DISCUSSIONS

In order to assess therapeutic and price benefits of multiple strengths of IVIG, 29 days extensive field work was undertaken covering six major cities of India.
Tier 1 cities- Bengaluru, Mumbai, NCR
Tier 2 cities- Jaipur, Trivandrum, Cochin

Of the total 60 hospitals in West, South and North, 53 hospitals were responsive, and of the 298 doctors, 287 of them gave productive data.
Purchase managers were also met of various hospitals of which 22 were responsive.

### I. Sample distribution in various cities

| *City* | *No. of field working days* | *Responsive hospitals* | *Responsive doctors* |
|---|---|---|---|
| Mumbai | 7 | 13 | 53 |
| NCR | 9 | 15 | 85 |
| Bengaluru | 5 | 7 | 29 |
| Jaipur | 2 | 6 | 28 |
| Trivandrum | 2 | 5 | 36 |
| Cochin | 4 | 7 | 55 |

*Table 3: Responsive hospitals and doctors in different cities*
*Total hospitals covered were 60, of which 53 hospitals were responsive and of the 298 doctors visited, 287 provided constructive data.*

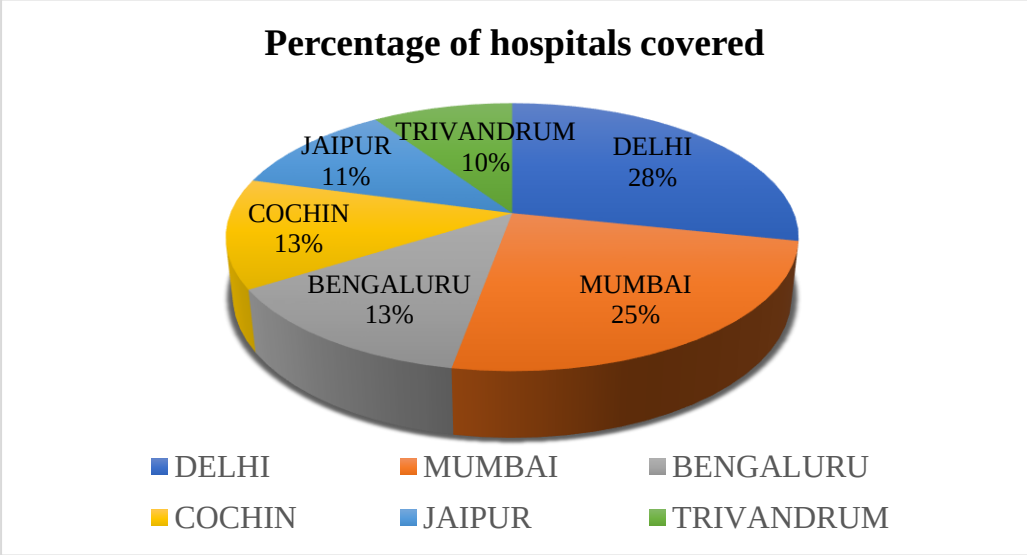



*Fig 1: Percentage of hospitals covered in various cities*
*This represent data contribution of individual city, of which Delhi and Mumbai forms the major break apart of data.*

## II. Doctors covered in various specialties in different cities

IVIG possesses usage in various specialties such as Neurology, Pediatrics, Rheumatology, Intensivist, Dermatology, Internal Medicine, Hematology and Nephrology.
After interaction with various purchase managers, it was found that usage of IVIG is found to be maximum by neurologists. Pediatricians also use IVIG extensively and its usage is increasing for off label indications as well.

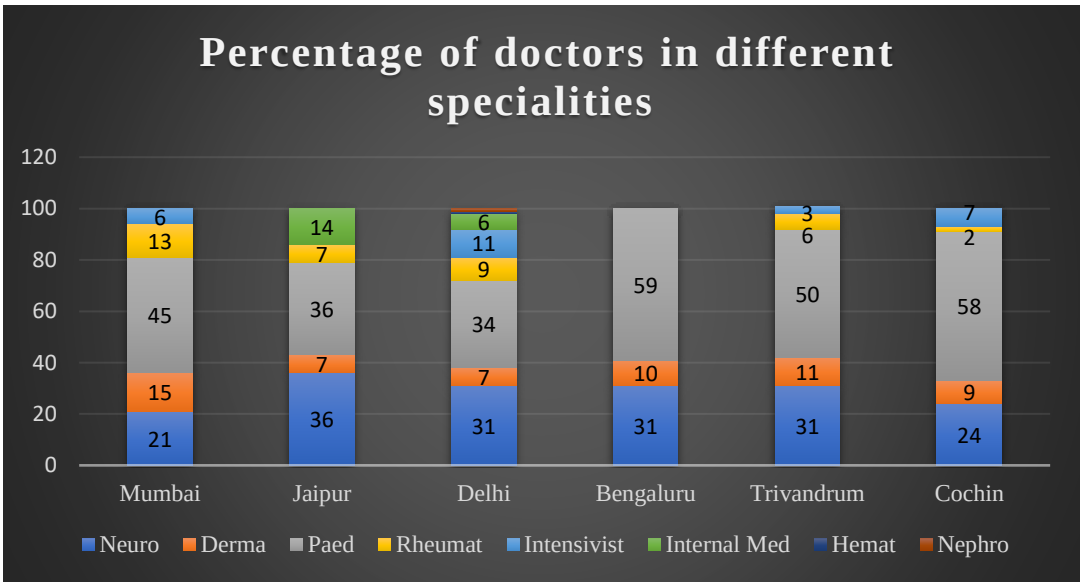



*Fig 2: City wise segregation of different specialties of doctors*

*Of the total doctors covered 80 were neurologists, 28 dermatologists, 130 pediatricians and neonatologists, 20 rheumatologists, 17 intensivists which includes PICU as well as NICU, 9 internal medicine, 1 hematologist and 1 nephrologist*

## III. Usage frequency of IVIG

| % Usage frequency | Mumbai | Jaipur | Delhi | Bengaluru | Trivandrum | Cochin |
|---|---|---|---|---|---|---|
| Very Frequently | 19 | 25 | 27 | 10 | 33 | **40** |
| Frequently | **53** | **46** | **49** | **62** | 22 | 31 |
| Occasionally | 9 | 14 | 8 | 10 | 3 | 20 |
| Rarely | 17 | 11 | 12 | 17 | **42** | 9 |
| Never | 2 | 4 | 4 | 0 | 0 | 0 |

*Table 4a:Usage pattern of IVIG in different cities*
*IVIG usage is dominant in almost all cities with usage pattern of once or more in a month. Trivandrum and Cochin had lesser frequency usage as compared to other cities.*

| % Usage frequency | Neurology | Dermatology | Paediatrics | Rheumatology | Internal Medicine | Intensivist |
|---|---|---|---|---|---|---|
| Very Frequently | 39 | 0 | 27 | 15 | 0 | **65** |
| Frequently | **48** | 21 | **42** | **60** | **56** | 35 |
| Occasionally | 9 | 21 | 12 | 10 | 11 | 0 |
| Rarely | 5 | **46** | 18 | 15 | 33 | 0 |
| Never | 0 | 11 | 2 | 0 | 0 | 0 |

*Table 4b:Usage pattern of IVIG in different specialties*
*IVIG is used thrice or more in a month by intensivists, and once or more in a month by neurologist, pediatricians, rheumatologists and doctors of internal medicine. Dermatologists usage was rare accounting to once in six months.*

For Fig 3a and 3b:
Very Frequently- Three or more times in a month
Frequently- Once or more in a month
Occasionally- Once in three months
Rarely- Once in six months

## IV. Usage indication for IVIg in different specialties of various cities.

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Paediatrics** | Sepsis | GBS | Kawasaki | ITP | NAT | Myasthenia Crisis | ADEM | Dermatomyositis |
| | 11 | 19 | 13 | 18 | 4 | 4 | 4 | 2 |

| | | | | | |
|---|---|---|---|---|---|
| **Neurology** | GBS | M. Crisis | ADEM | MMN | CIDP |
| | 11 | 6 | 8 | 4 | 7 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Intensivist** | Kawasaki | GBS | SLE | ITP | ADEM | Post bone marrow transplant |
| | 1 | 2 | 1 | 2 | 1 | 1 |

| | | | | | |
|---|---|---|---|---|---|
| **Dermatology** | Stevenson Johnson Syndrome | Atopic Dermatitis | Toxic Epidermal Necrolysis | Pemphigus | Vasculitis |
| | 7 | 3 | 3 | 3 | 2 |

| | | | |
|---|---|---|---|
| **Rheumatology** | Dermatomyositis | Vasculitis | SLE |
| | 6 | 3 | 5 |

*Table 5a: Indications in different specialties of Mumbai for IVIg usage*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Paediatrics** | GBS | ITP | Septicaemia | ADEM | Refractory epilepsy | CIDP | Myasthenia Crisis | Kawasaki |
| | 10 | 3 | 5 | 2 | 1 | 2 | 2 | 4 |

| | | | | | |
|---|---|---|---|---|---|
| **Neurology** | GBS | CIDP | ADEM | Myasthenia Crisis | MMN |
| | 10 | 2 | 3 | 6 | 3 |

| | | | | |
|---|---|---|---|---|
| **Rheumatology** | Vasculitis | ITP | GBS | CVID |
| | 1 | 1 | 1 | 1 |

| | | | |
|---|---|---|---|
| **Internal Medicine** | GBS | CVID | Sepsis |
| | 4 | 2 | 1 |

| | | |
|---|---|---|
| **Dermatology** | Pemphigus | Toxic epidermal necrolysis |
| | 1 | 1 |

*Table 5b: Indications in different specialties of Jaipur for IVIg usage*

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Paediatrics** | GBS | ITP | ADEM | Septicaemia | Kawasaki | Dermatomyositis | Myasthenia Crisis | Multiple Sclerosis |
| | 24 | 13 | 6 | 9 | 19 | 1 | 6 | 2 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Neurology** | GBS | Myasthenia Crisis | ADEM | MMN | CIDP | Stiff Person | Refractory epilepsy |
| | 26 | 21 | 11 | 5 | 11 | 3 | 2 |

| | | | | | |
|---|---|---|---|---|---|
| **Intensivist** | Kawasaki | GBS | ITP | Sepsis | Post bone marrow transplant |
| | 5 | 5 | 7 | 4 | 2 |

| | | | | |
|---|---|---|---|---|
| **Dermatology** | Toxic epidermal necrolysis | Dermatomyositis | Vasculitis | Pemphigus |
| | 4 | 2 | 2 | 2 |

| | | | |
|---|---|---|---|
| **Internal Medicine** | GBS | CVID | Sepsis |
| | 5 | 3 | 1 |

*Table 5c: Indications in different specialties of Delhi for IVIg usage*

| | | | | | | |
|---|---|---|---|---|---|---|
| **Paediatrics** | ITP | Kawasaki | GBS | Sepsis | Rh incompatibility | ADEM |
| | 10 | 8 | 10 | 6 | 4 | 2 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Neurology** | GBS | Myasthenia Crisis | CIDP | ADEM | MMN | Multiple Sclerosis |
| | 9 | 7 | 9 | 5 | 2 | 1 |

| | | | | |
|---|---|---|---|---|
| **Dermatology** | Stevenson Johnson Syndrome | Toxic epidermal necrolysis | Pemphigus | SLE |
| | 3 | 1 | 1 | 1 |

*Table 5d: Indications in different specialties of Bengaluru for IVIg usage*

| | | | | | |
|---|---|---|---|---|---|
| **Neurology** | GBS | Myasthenia Crisis | ADEM | CIDP | MMN |
| | 11 | 9 | 9 | 4 | 2 |

| | | | | | |
|---|---|---|---|---|---|
| **Paediatrics** | GBS | ADEM | Kawasaki | ITP | Sepsis |
| | 12 | 4 | 13 | 8 | 1 |

| | | | | | |
|---|---|---|---|---|---|
| **Intensivist** | GBS | ADEM | CIDP | Myasthenia Crisis | Multiple Sclerosis |
| | 1 | 1 | 1 | 1 | 1 |

| | | | | | |
|---|---|---|---|---|---|
| **Dermatology** | Stevenson Johnson Syndrome | Toxic epidermal necrolysis | Pemphigus | SLE | Vasculitis |
| | 4 | 1 | 1 | 3 | 1 |

*Table 5e: Indications in different specialties of Trivandrum for IVIg usage*

| | | | | | |
|---|---|---|---|---|---|
| **Paediatrics** | Kawasaki | ITP | GBS | ADEM | Sepsis |
| | 21 | 6 | 18 | 7 | 10 |

| | | | | | |
|---|---|---|---|---|---|
| **Neurology** | GBS | Myasthenia Crisis | ADEM | Multiple Sclerosis | CIDP |
| | 13 | 7 | 10 | 2 | 5 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Intensivist** | Kawasaki | ITP | GBS | Sepsis | Myasthenia Crisis | Rh incompatibility |
| | 3 | 1 | 1 | 4 | 1 | 2 |

| | | | | |
|---|---|---|---|---|
| **Rheumatology** | Stevenson Johnson | Dermatomyositis | SLE | Vasculitis |
| | 1 | 1 | 1 | 1 |

| | | |
|---|---|---|
| **Dermatology** | Toxic epidermal necrolysis | Stevenson Johnson Syndrome |
| | 4 | 3 |

*Table 5f: Indications in different specialties of Cochin for IVIg usage*

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Paediatrics** | GBS | Kawasaki | ITP | Sepsis | ADEM | M. Crisis | NAT | Rh incompatibility | Dermatomyositis | Multiple Sclerosis |
| | 93 | 78 | 58 | 42 | 25 | 6 | 4 | 4 | 3 | 2 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Intensivist** | Kawasaki | ITP | GBS | Sepsis | M. Crisis | Rh incompatibility | ADEM | Post bone marrow transplant |
| | 9 | 10 | 9 | 8 | 2 | 2 | 3 | 3 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Neurology** | GBS | Myasthenia Crisis | ADEM | CIDP | MMN | Multiple Sclerosis | Refractory epilepsy |
| | 80 | 56 | 46 | 38 | 16 | 3 | 2 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Dermatology** | Stevenson Johnson Syndrome | Toxic epidermal necrolysis | Pemphigus | Vasculitis | SLE | Atopic Dermatitis |
| | 17 | 14 | 8 | 5 | 4 | 3 |

| **Rheumatology** | Stevenson Johnson Syndrome | Dermatomyositis | SLE | Vasculitis |
|---|---|---|---|---|
| | 1 | 12 | 14 | 13 |

| **Internal Medicine** | GBS | CVID | Sepsis |
|---|---|---|---|
| | 9 | 5 | 2 |

*Table 5g: Indications in different specialties for IVIg usage in all the cities covered*

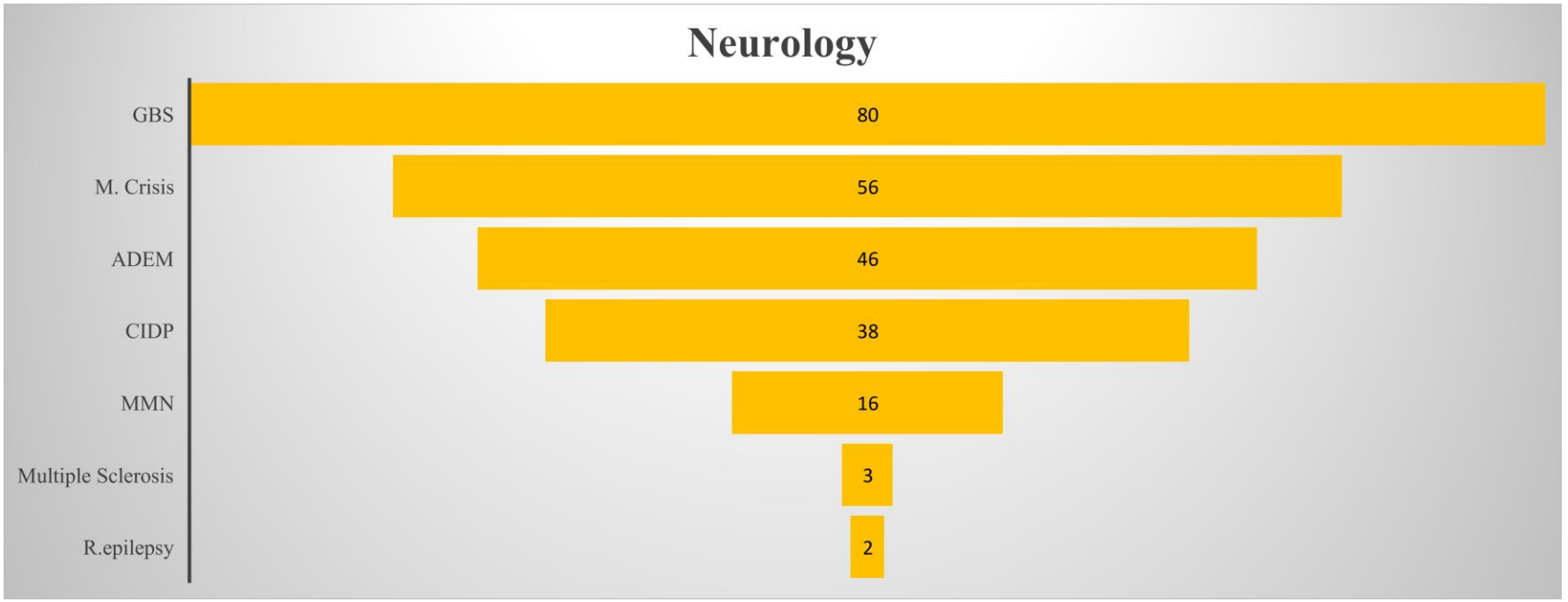



*Fig 3 : Usage indications of IVIg in Neurology in all the cities covered*

Of all the neurologists interacted, IVIg was being prescribed for the cases of GBS. It was interviewed that both plasma exchange and IVIg act as effective immunotherapies if given during first few weeks of GBS progression. Plasma exchange being comparatively affordable for major population when compared to IVIg, but its need for intervention positions it as not being the choicest therapy. Myasthenic Crisis being the severe form of myasthenia gravis and a life-threatening disease requires administration of IVIg. The first line treatment for CIDP is usually corticosteroids, IVIg/PLEX are preferred as second line treatment options. Methylprednisolone is the first line treatment for acute disseminated encephalomyelitis (ADEM), and highly severe cases are left to be treated with IVIg/PLEX. Similar is the case with multiple sclerosis and refractory epilepsy wherein IVIg is the second line treatment. Monoclonal antibodies are also preferred, but substantial correlation for its usage could not be drawn from the available data.

Other indications in neurology for which IVIg has been used by doctors are as:

- Paraneoplastic
- Paraprotein associated demyelinating neuropathy
- Stiff person syndrome
- Vasculitis
- Paraneoplastic cerebellar degeneration (PCD)
- Neuroblastoma with opsonization
- Diabetic amyotrophy
- Osmotic demyelination syndrome (ODS)
- Acute motor axonal neuropathy (AMAN)
- Acute motor and sensory axonal neuropathy (AMSAN)
- Multiple myositis

It has been found that there is a widespread usage of IVIg in off label indications as well. After interacting with 80 neurologists, it was concluded that IVIg acts as first line choice of drug for hard core indications such as Myasthenia Crisis, GBS. Some doctors even preferred it for MMNCB as well as PCD. IVIg and PLEX were noted to have similar efficacy, the only difference for preference was discussed over the affordability of the former immunotherapy. In erstwhile indications, its usage widely depends on disease condition of the patient. For CIDP, opinion of doctors differed for first line drug, but it could be concluded that being chronic in nature IVIg doesn't respond effectively and hence IVIg doesn't remain the choicest drug of usage.

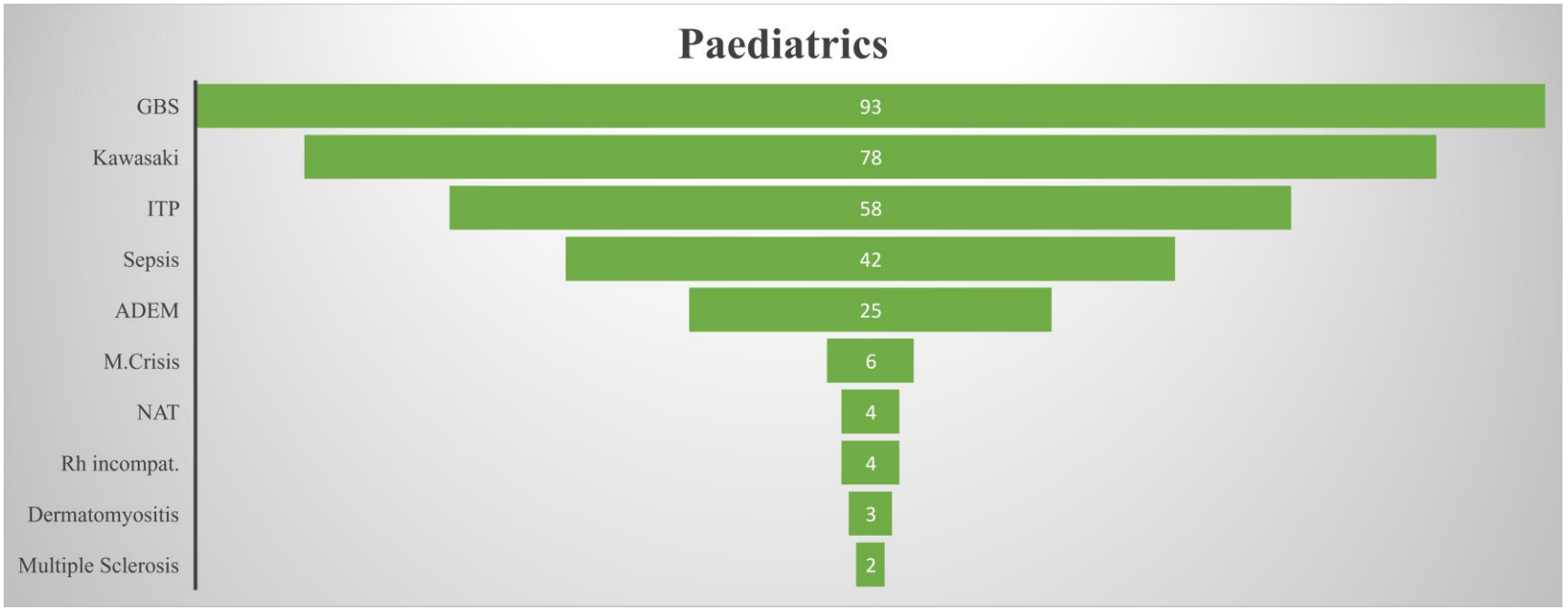



*Fig 4 : Usage indications of IVIg in Paediatrics in all the cities covered*

Of the entire 130 pediatricians and neonatologists (neurologists, hematologists, rheumatologists) interacted, the highest incidence for prescription of IVIg was noted in GBS, Kawasaki and Immune thrombocytopenic purpura. IVIg preference for these three indications was found to be promising and as first line therapy. GBS and Kawasaki both were reported to be clustering in nature. Owed to improved awareness of Kawasaki disease, its diagnosis has been increased over the past few years. But it could not be strongly correlated that whether the incidence of Kawasaki disease has increased or is it only its improved diagnosis, with greater number of doctors favoring the latter reason. For septicemia antibiotics are first line drugs however when it progresses to being a life threatening, IVIg is extensively used.

In pediatrics, it has also been found to be used in cases of ADEM, myasthenia crisis, neonatal alloimmune thrombocytopenic purpura, dermatomyositis and multiple sclerosis. It has an noteworthy usage in cases of Rh incompatibility as well, in mild cases phototherapy remains line of treatment and in severe cases blood transfusion is recommended and IVIg.

Other indications in pediatrics for which IVIg usage is preferred:

- Hemolytic jaundice
- Autoimmune hemophilia
- Autoimmune neutropenia
- Streptococcal toxic shock syndrome
- Hypogammaglobulinemia
- Agammaglobulinemia
- ANCA Vasculitis
- Viral myocarditis
- Systemic lupus erythematosus with neurological disorders
- Anti MOG antibodies
- Neuromyelitis optica spectrum disorder (NMOSD)
- Common variable immunodeficiency
- Severe combined immunodeficiency
- Pediatric autoimmune neuropsychiatric disorder (PANDAS)
- Refractory/Intractable epilepsy
- Post chicken pox contact if *Varicella Zoster* is unavailable
- Polyradioneuropathy
- Congenital immunodeficiency
- Primary immune deficiency
- Hemolytic anemia
- Neonatal jaundice
- ADAMS
- Post viral demyelination
- Anti-NMDA receptor encephalitis
- Vasculitis-polyarthritis syndrome
- Hyperbilirubinemia

PID- B cell immunomodulatory-monthly IVIg is given
T cell immunomodulatory- Bone marrow transplant and then IVIg is prescribed.

Additional learning was that IVIg could be given in active infections whereas steroids are usually contraindicated.

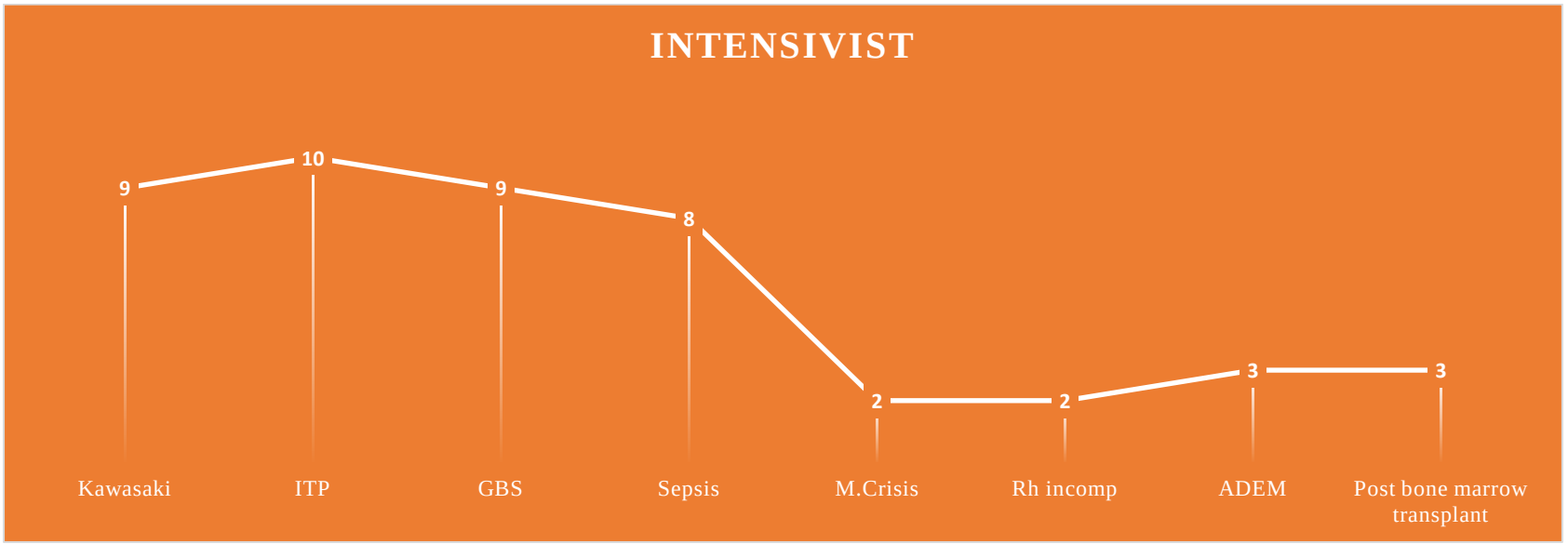
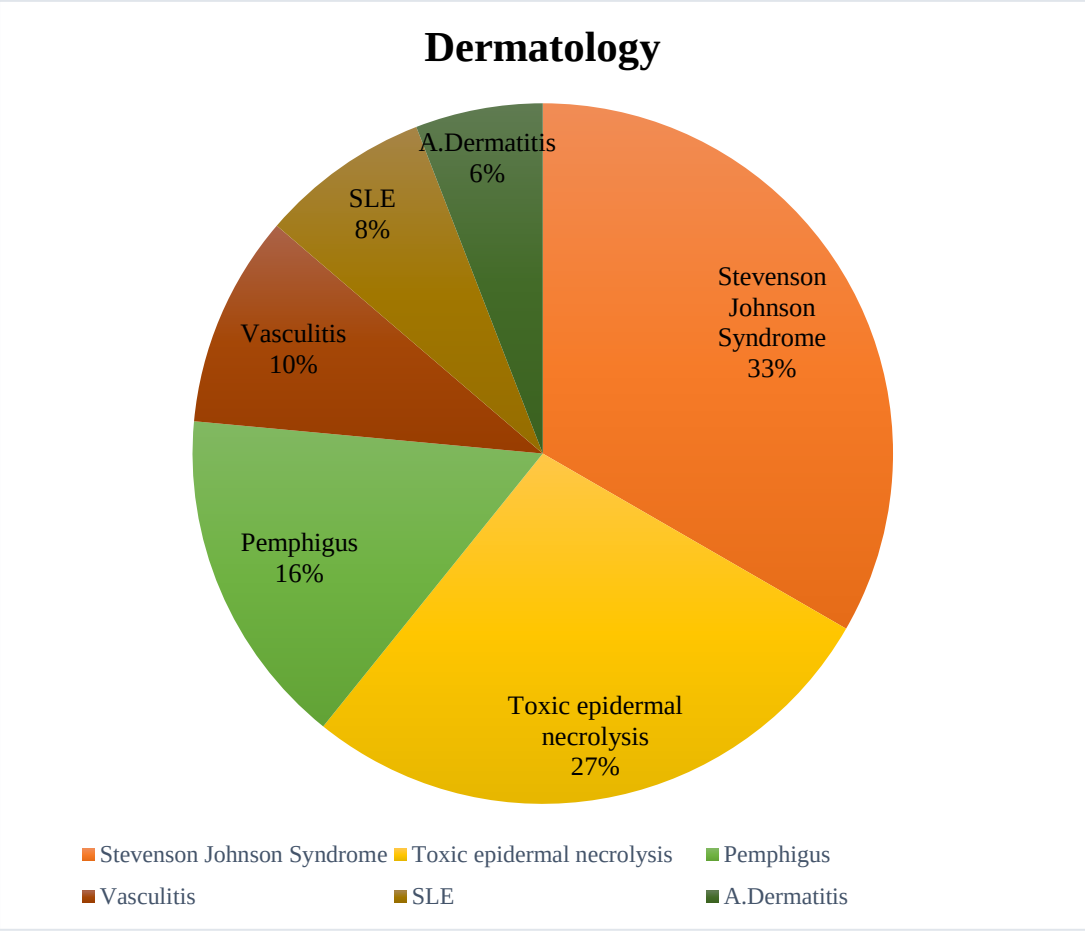



*Fig 5: Usage indications of IVIg by Intensivists in all the cities covered*

Intensivist of adults, pediatrics (PICU), neonatology (NICU) claimed usage of IVIg in various indications, predominant of which were Kawasaki disease, ITP, GBS, worsened sepsis. It moreover found its usage in post bone marrow transplant, myasthenia crisis, Rh incompatibility and ADEM. For Kawasaki disease, GBS and ITP was first line therapy and for rest its usage was determined on disease condition of the patient, and failure of first therapies to respond.

Other indications for IVIg usage were:

- Hepatitis B
- Viral meningitis
- Multiple sclerosis
- CIDP
- Neonatal alloimmune thrombocytopenia
- Autoimmune neutropenia




The usage of IVIg is not predominant in dermatology, its usage is only engaged in severe allergic reactions or acute skin failure. The first line treatment therapy in dermatology is ordinarily corticosteroids, depending upon disease conditions.
IVIg is retained as last treatment option in cases of Stevenson Johnson Syndrome, toxic epidermal necrolysis, pemphigus, vasculitis, SLE and in severe cases of atopic dermatitis.

*Fig 6: Usage indications of IVIg by Dermatologists in all the cities covered*

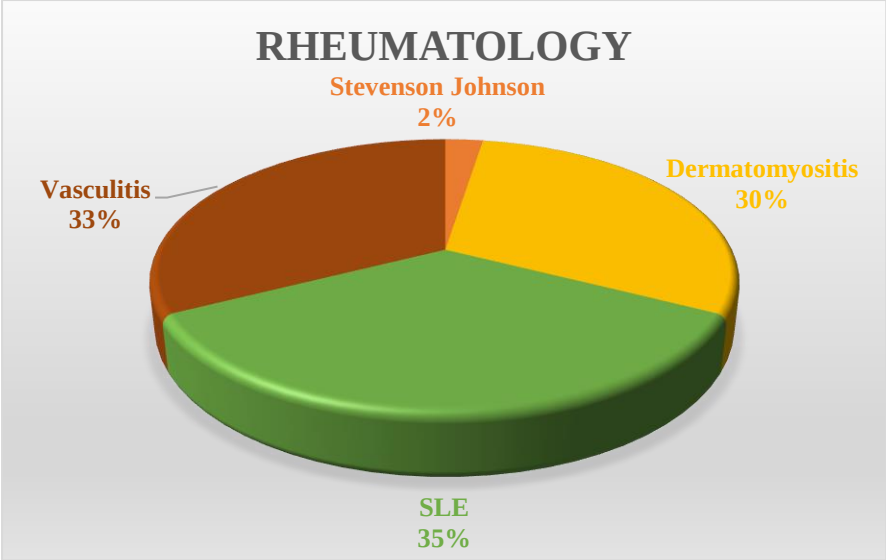



*Fig 7: Usage indications of IVIg by Rheumatologists*

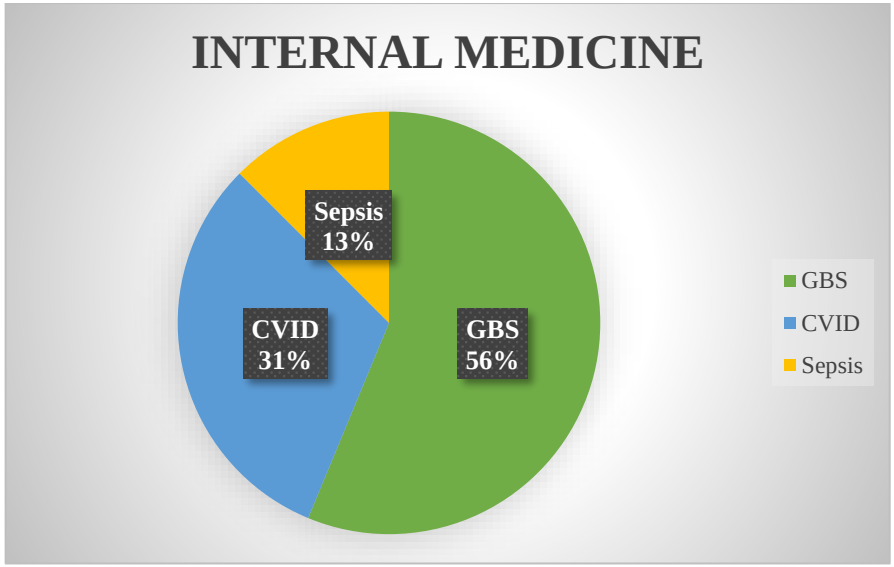



*Fig 8: Usage indications of IVIg by Internal Medicine*

IVIg is employed in treatment of inflammatory muscle diseases which is dermatomyositis, SLE, vasculitis and Stevenson Johnson Syndrome. It is established to be safer in pregnancy and breast feeding as well. For SLE, corticosteroids and monoclonal antibodies are preferred as first line drug by majority of the doctors. While interaction with some doctors, it was found that since affordability is the major issue dosage of IVIg was reduced to 40%, although no such literature was found which signified therapeutic effectiveness of IVIg to half of its dosage.

Doctors of internal medicine were likewise found using IVIg. These indications were GBS forming the major block, common variable immune deficiency and sepsis. For the later indication, IVIg doesn't form the first line drug.

## V. Usage pattern of multiple strengths (5g/100ml, 10g/100ml, 2.5g/50ml) of IVIg in different strengths

West & South

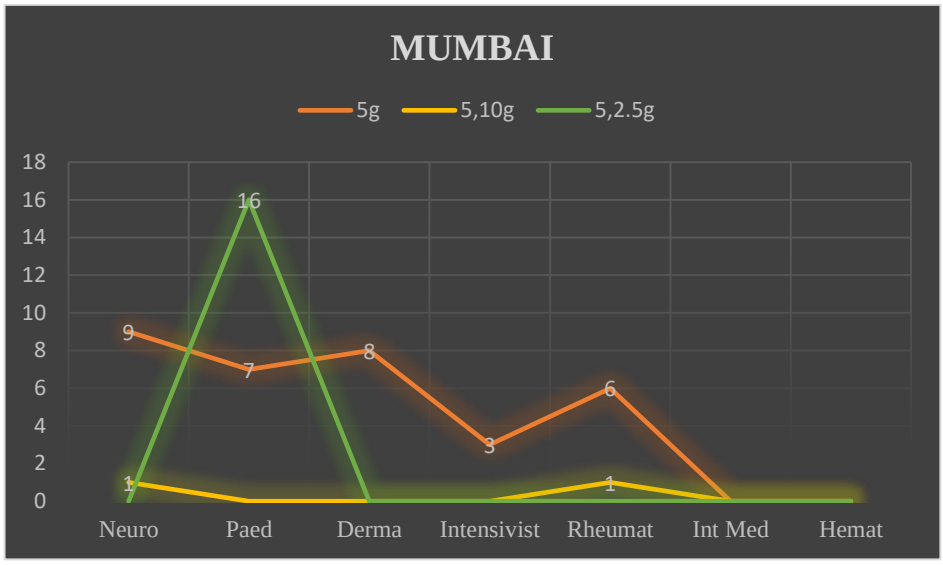



*Fig 9a: Multiple strengths of IVIg usage in Mumbai*
*Usage of 5g/100ml was found greater in all specialties*
*Usage of 2.5g/50ml was found more with Pediatricians*

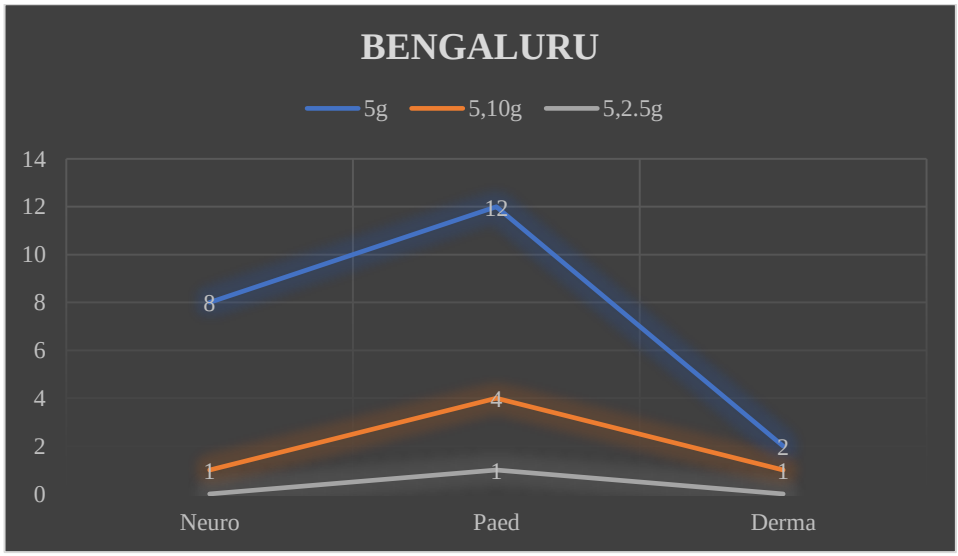



*Fig 9b: Multiple strengths of IVIg usage in Bengaluru*
*Usage of 5g/100ml was found greater in Bengaluru*

North:

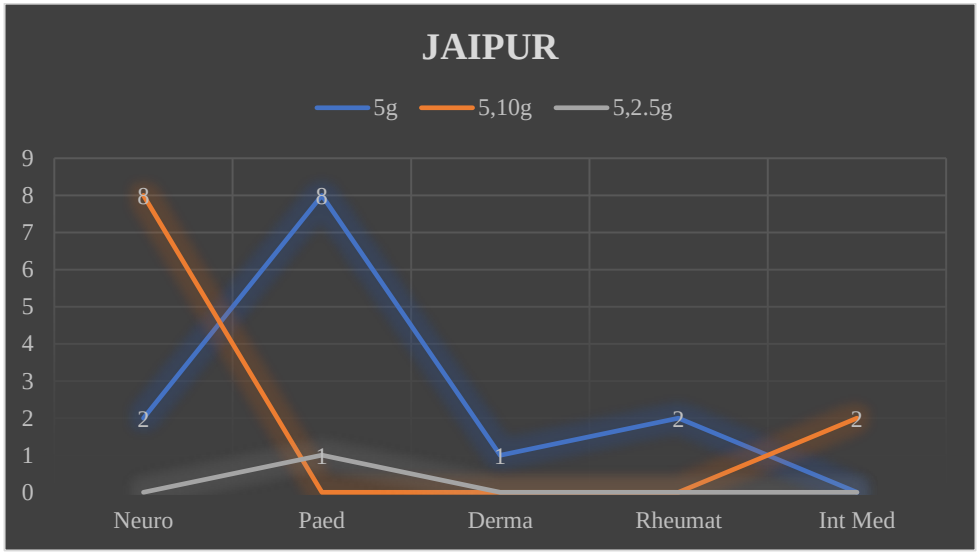



*Fig 9c : Multiple strengths of IVIg usage in Jaipur*
*Usage of 10g/100ml was found in Jaipur by neurologists along with 5g/100ml*

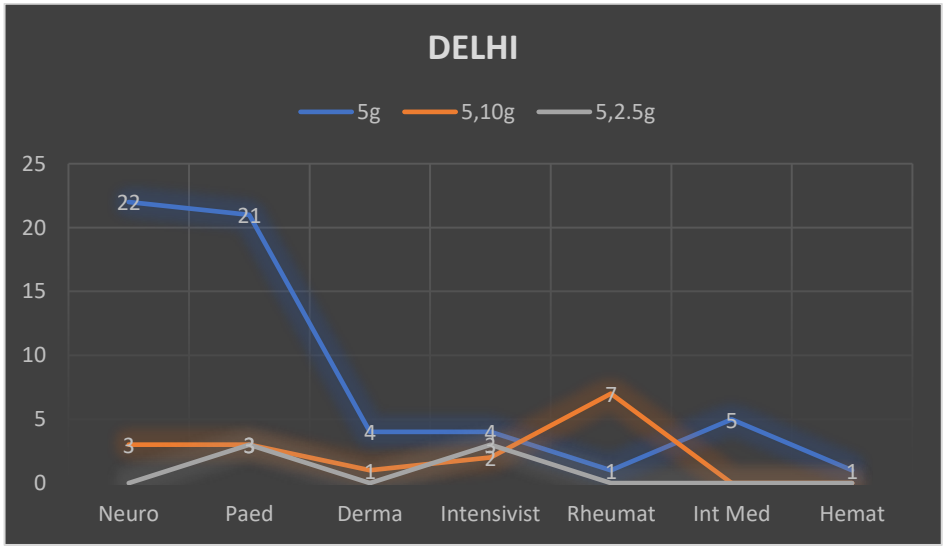



*Fig 9d : Multiple strengths of IVIg usage in Delhi*
*Usage of 5g/100ml was found highest by neurologists and pediatricians*

South:

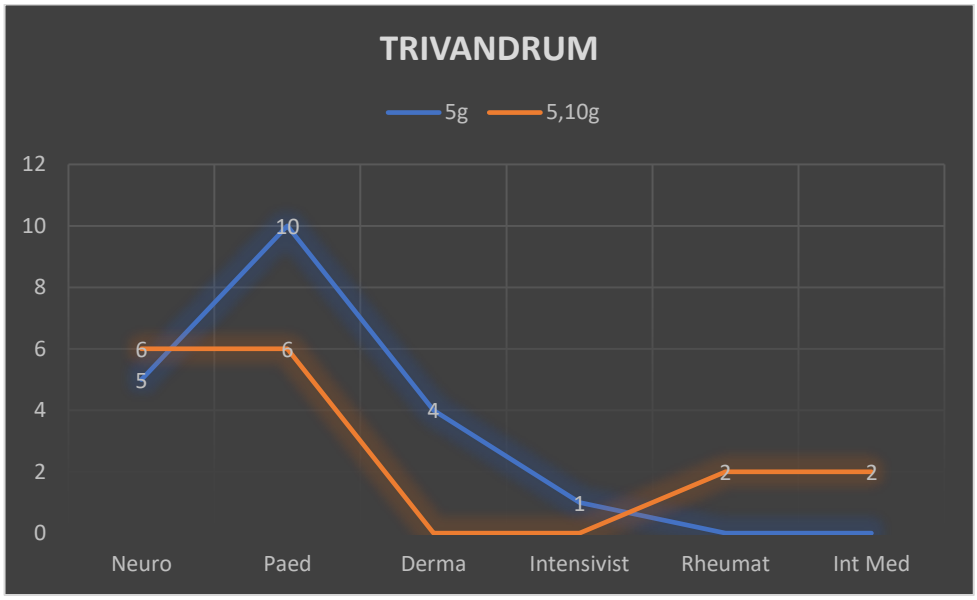



*Fig 9e : Multiple strengths of IVIg usage in Trivandrum*
*Usage of 5g/100ml and 10g/100ml both was found in Trivandrum*

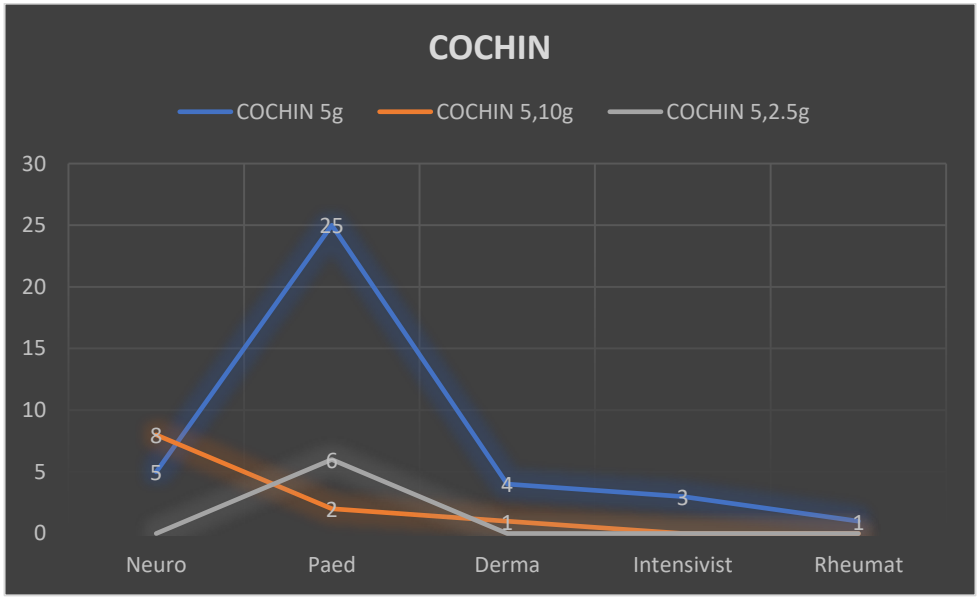



*Fig 9f : Multiple strengths of IVIg usage in Cochin*
*Usage of 5g/100ml was found highest and also 10g/100ml was found being used in Cochin*

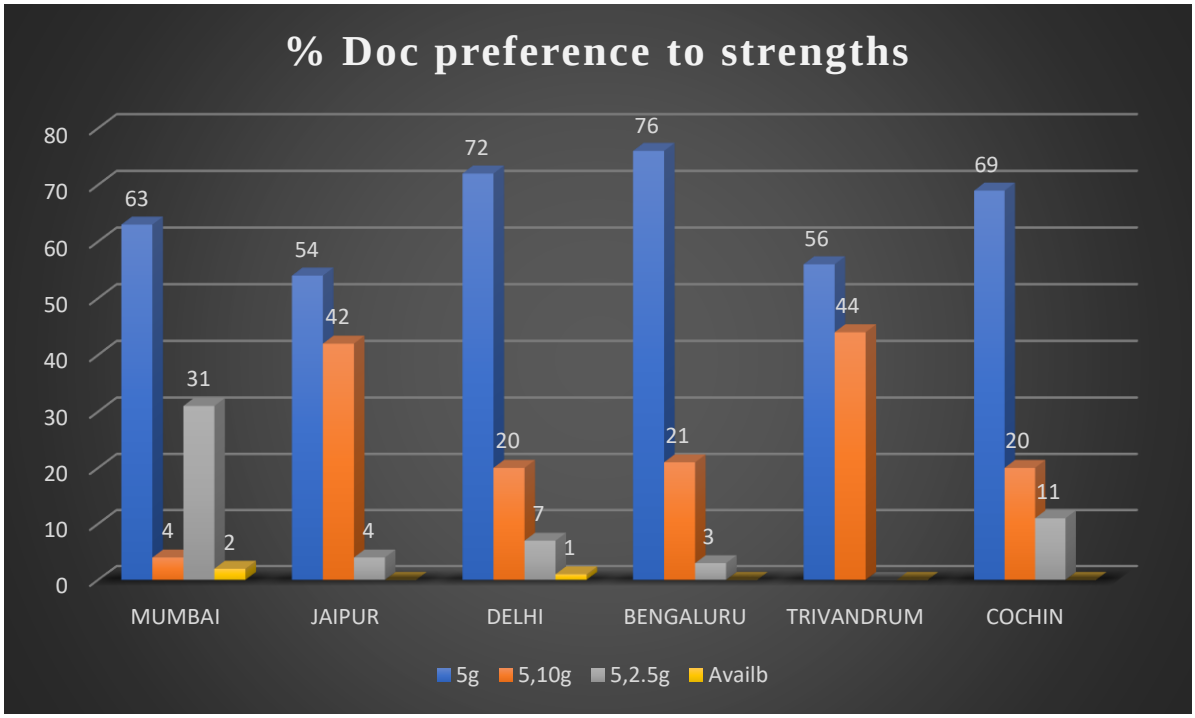



*Fig 9g : Preference of doctors for multiple strengths of IVIg in different cities of India*

The consumption of 5g/100ml was found premier in all cities when compared to other strengths. It was found that doctors in Mumbai were not using 10g/100ml in much quantity as equated to other cities. The cities like Trivandrum and Jaipur showed highest consumption of 10g/100ml. There was equal usage of 10g/100ml in Bengaluru, Delhi and Cochin.

Following interaction with doctors it was noted that, 10g/100ml being fresher to market had less usage as paralleled to its variant 5g/100ml. The former is building its place in market in terms of affordability, for it is more economical to shift to 10g/100ml. Some doctors disclosed concern of hyper viscosity and stroke with 10g/100ml. This strength was preferred in patients suffering from renal failure and hence require lesser fluid volume.

The usage of 2.5g/50ml was found more in specialties of pediatrics and neonatology. Availability being an issue in some hospitals would make doctors shift to the strengths that could be easily available.

After interaction with purchase managers as well, it was found that Intas had a sturdier hold in Jaipur. Its presence was also felt in Delhi, Bengaluru, Trivandrum and Cochin. Reliance had prime share of prescriptions in all the cities. PlasmaGen was found in Delhi and Bengaluru, with other cities a lesser brand recall of this company was found.

## VI. Treatment mode of IVIg

IVIg sparks its usage as curative, supportive and replacement therapy in various indications. Following figures give a glance of its usage as different treatment modes.

a. Curative therapy

- GBS
- ADEM
- Kawasaki Disease
- Multiple Sclerosis

b. Supportive therapy

- Neonatal Sepsis
- Immune thrombocytopenic purpura
- Stevenson Johnson Syndrome
- Systemic Lupus Erythematosus
- Vasculitis
- Dermatomyositis

c. Replacement therapy

- CVID
- PID

IVIg the immunomodulator is immensely employed in various specialties to treat several immune system disorders whether genetic or acquired in nature. If affordability had not been a major issue, it would not have found a switch with plasmapheresis, which is therapeutically as effective as IVIg, but its need of intervention restrains the doctors from its usage.
Most IVIg reactions are rate limiting and mild ordinarily being fever, rashes, aseptic meningitis and chills. The patients normally recover from these side effects on their own. As a precautionary measure, IVIg is frequently infused at a slower rate for first 30 minutes, some prefer the slower infusion till 1 hour as well. On occurrence of side effects, dose is usually titrated and the patient is made to well hydrate to avoid the incident of aseptic meningitis. The cases of renal failure were found in patients in events of acute kidney insufficiency. Exacerbation of adverse events occur in patients with IgA deficiency, thus level of IgA in IVIg remains of utmost importance to physicians.
The use of sub-cutaneous IVIg is employed in some developed countries, although it has not yet been introduced in India.
Excipients in IVIg as well play a major role in its stability as well as its usage in complicated cases. They are added to prevent aggregation of purified IgG which may lead to adverse reactions. Doctors did not had much say in its choice, of all the doctors interacted only four of them opinionated about it, stating their preference to be amino acids, glycine and maltose.

On interaction with the purchase managers it was found out that specialty of neurology had maximum usage of IVIg, next being the paediatrics. On an average 1-2 doses of IVIg were maintained in the hospital pharmacy.

## CONCLUSION

IVIg is used for broad array of indications because of its diverse therapeutic mechanisms. It is widely used as curative, supportive and replacement therapy. Reliance, the brand leader with its product Immunorel 5g/100ml enjoys eclectic prescription, but companies such as Intas are positioning their 10g/100ml product in terms of affordability to become the choicest drug of prescription. IVIg the immunomodulating therapy has an equal efficacy as compared to plasmapheresis, but the need of intervention in latter one is cumbersome, offering IVIg to enjoy supreme position if affordability is not a concern.
On an average 1-2 doses of IVIg are maintained in the hospital pharmacies and have faster refills whenever required. Neurology department of the hospital has maximum consumption of IVIg and the choice of brand usage on an whole depended upon central formulatory. In government hospitals, there is lesser stress towards one brand usage.
It was realized that brand equity of the competitor of PlasmaGen that is Reliance was greater in almost all the cities covered.

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# Questionnaire on Multiple Strengths of IVIG and Excipients

Name of Doctor : Specialty:

Hospital : Date :

**1. What is the frequency of usage of IVIG**

- Very frequently (3 or more times in a month)
- Frequently (once or more in a month)
- Occasionally (once in 3 months)
- Rarely (once in 6 months)
- Never

**2. Indications for which IVIG is prescribed maximum and for what priority conditions:**

**Neurology**

- Guillain-Barre Syndrome (GBS)
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
- Multifocal Motor Neuropathy
- Myasthenia Gravis
- Stiff Person Syndrome
- Acute Disseminated Encephalomyelitis (ADEM)
- Multiple Sclerosis
- Other Neurological Conditions _____

**Hematology**

- Idiopathic Thrombocytopenic Purpura (ITP)
- Myeloma
- Chronic Lymphocytic Leukemia
- Post Bone Marrow Transplantation (GvHD)
- Auto-immune Neutropenia
- Immune Hemolytic Anemia
- Others _____

**Pediatrics**

- ☐ Primary Immuno Deficiency (PID)
- ☐ Idiopathic Thrombocytopenic Purpura (ITP)
- ☐ Kawasaki Disease
- ☐ Neonatal Sepsis
- ☐ Neonatal Alloimmune Thrombocytopenia
- ☐ Other _____

**Dermatology**

- ☐ Dermatomyositis & Polymyositis
- ☐ Stevens Johnson Syndrome
- ☐ Toxic epidermal necrolysis
- ☐ Blistering diseases
- ☐ Immune urticaria
- ☐ Atopic dermatitis
- ☐ Scleromyxoedema
- ☐ Other _____

**Nephrology, Rheumatology, Ophthalmology and Other**

- ☐ ANCA Vasculitis
- ☐ Systemic lupus erythematosus
- ☐ Streptococcal toxic shock syndrome
- ☐ Birdshot retinochoroidiopathy
- ☐ Autoimmune uveitis
- ☐ Other _____

**3. What is the strength of IVIG being preferred**

- ☐ 10g/100ml
- ☐ 5g/100ml
- ☐ 2.5g/100ml
- ☐ 0.5g/100ml

**Why**_____

_____

**4. Preference of substitutes over IVIG**

- ☐ Corticosteroids
- ☐ Plasma-exchange
- ☐ Monoclonal Antibodies

□ Others _____

**5. The preference criteria for IVIG is dependent on**

□ Safety
□ Availability
□ Affordability
□ Efficacy

**6. IVIG is preferred as**

□ Replacement therapy
□ Curative therapy
□ Supportive therapy

_____

_____

**7. What are the adverse reactions commonly being encountered with prescribed IVIG**

_____

_____

_____

**8. If choice is given then what base/excipient of IVIG would be preferred**

- *Sugars*
  - □ Sucrose
  - □ Glucose
  - □ Maltose
- *Polyols*
  - □ Sorbitol
- *Amino Acids*
  - □ Glycine
  - □ L – Proline

***Thanks for your participation in this survey!***

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# Questionnaire on Hospital Usage of IVIG

Name of Purchase Manager: Date :
Designation: Hospital:

**1. On an average of per month, what is the minimum inventory maintained for IVIG**

- □ _____ vials for 10g/100ml
- □ _____ vials for 5g/100ml
- □ _____ vials for 2.5g/100ml
- □ _____ vials for 0.5g/100ml

**2. What is the percentage of vials being consumed per month for the following strengths of IVIG**

- □ 10g/100ml _____
- □ 5g/100ml _____
- □ 2.5g/100ml _____
- □ 0.5g/100ml _____

**3. For which department there is highest consumption of IVIG**

- □ Neurology
- □ Hematology
- □ Intensivist
- □ Pediatrics
- □ Rheumatology
- □ Dermatology
- □ Transplant
- □ Other _____

**4. What are the companies from whom you procure IVIG**

- □ Immunorel
- □ Globucel
- □ PlasmaGob
- □ Seroglobulin
- □ Genexglob
- □ Emglobulin
- □ Igwok
- □ Other _____

5. **Which brand of IVIG is preferred most and in what percentage**

_____

- 100-91%
- 90-81%
- 80-71%
- 70-61%
- 60-51%

6. **Decision making authority for IVIG purchase depends upon**

- Purchase Officer
- Head of _____ department
- Central Formulatory
- Stockist
- Other _____

***Thanks for your participation in this survey!***