

Intravenous Immunoglobulin (IVIg) Supply Availability

June 4, 2020

GREATER NEW YORK HOSPITAL ASSOCIATION

*Over 100 years of helping hospitals deliver the
finest patient care in the most cost-effective way.*

Welcome & Agenda

Welcome & Background

- Jenna Mandel-Ricci, Vice President, Professional and Regulatory Affairs, GNYHA

IVIG Supply Landscape – Pre-COVID and Currently

- Kim Elmore, Senior Director, Pharmacy Contracting, Premier Inc.

Existing Structures Used to Manage the IVIG Supply

Patrick M. Schmidt, Chief Executive Officer, FFF Enterprises, Inc.

Resources on IVIG Stewardship & Conservation Strategies

- Sudha Narayanaswamy, Vice President, Pharmacy Practice, Acurity Inc.

Questions and Answers

Multisystem Inflammatory Syndrome in Children (MIS-C)

- First reported in the United Kingdom in late April
 - In early May, NYC DOHMH began receiving reports of children with similar symptoms
 - By May 12, NYS DOH had identified over 100 children with suspected cases statewide
 - Cases in NYS seem to be declining

- MIS-C is a condition where different body parts can become inflamed, including the heart, lungs, kidneys, brain, skin, eyes, or gastrointestinal organs.
 - Children with MIS-C may have a fever and various symptoms, including abdominal (gut) pain, vomiting, diarrhea, neck pain, rash, bloodshot eyes, or feeling extra tired.
 - What causes MIS-C is not yet known, however, many children with MIS-C had the virus that causes COVID-19 or had been around someone with COVID-19.

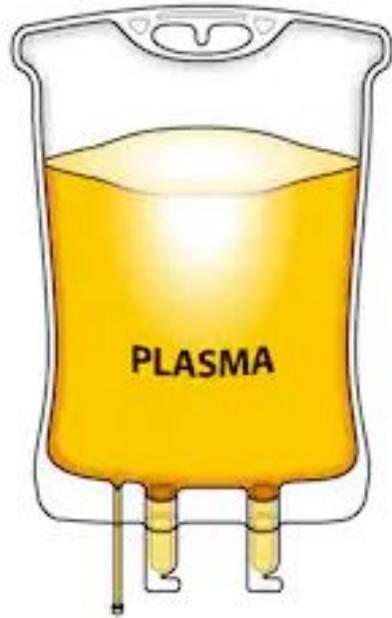
Role of Intravenous Immunoglobulin (IVIg) in Treatment of MIS-C

- Because condition is so new and so many bodily systems can be affected, there are significant practice variations based on clinical judgement
- However, because of its ability to suppress inflammation, IVIG has been broadly used to treat MIS-C

IVIG Supply Landscape

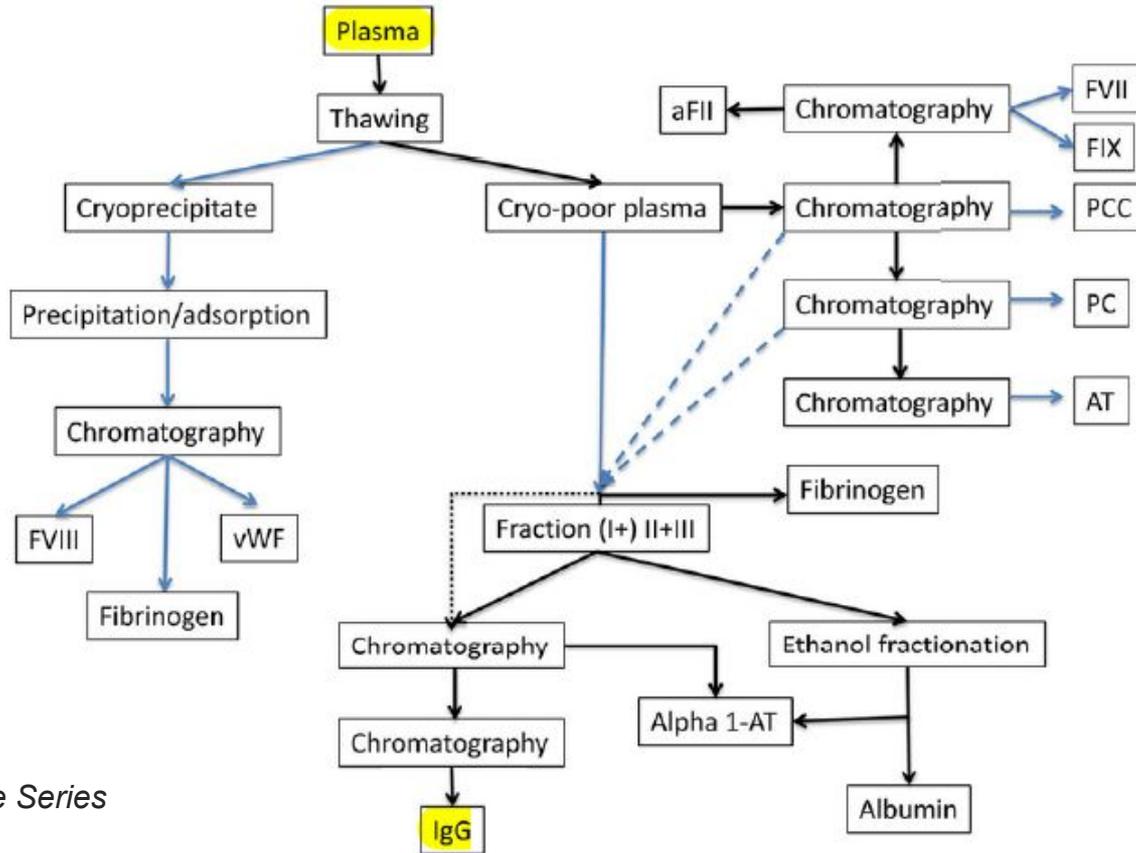
Kim Elmore, Senior Director, Pharmacy Contracting,
Premier Inc.

Key Therapeutic Proteins Purified from Donor Plasma



| Therapeutic Protein | Content per plasma liter |
|---|--------------------------|
| Immunoglobulin G (IgG) (IVIG/SCIG) | 3.5 – 5 g |
| Albumin | 25 g |
| Alpha-1 antitrypsin (AAT) | 0.15 – 0.30 g |
| C1 inhibitor (C1-INH) | 100 – 120 mg |
| Factor VIII | 180 – 200 IU |

The Plasma Fractionation Process



**IVI
G**

**IVIG /
SCIG**
gammunex-c
immune globulin injection (human), 10%
caprylate/chromatography purified

SCIG

Xembify®
(immune globulin subcutaneous
human-klhw) 20%

Grifols

CSL Behring

privigen®
Immune Globulin Intravenous
(Human), 10% Liquid

Hizentra®
Immune Globulin Subcutaneous
(Human) 20% Liquid

Takeda

**GAMMAGARD
S/D***

GAMMAGARD LIQUID
[Immune Globulin Infusion (Human)] 10%

Cuvitru
[Immune Globulin Subcutaneous (Human)] 20%

HyQvia
[Immune Globulin Infusion 10% (Human)
with Recombinant Human Hyaluronidase]

Octapharma

Immune Globulin Intravenous
(Human)
octagam® 10%
octagam® 5%

cutaquivig®
Immune Globulin Subcutaneous
(Human)-hipp, 16.5% solution

Kedrio

gammaked™
immune globulin injection (human), 10%
caprylate/chromatography purified

BP

Gammaflex 5% & 10%
Immune Globulin Intravenous

L
ADM

ASCENIV™
IMMUNE GLOBULIN INTRAVENOUS
(HUMAN) 10% LIQUID

BIVIGAM®
Immune Globulin Intravenous
(Human) 10% Liquid

*IgA less than 1 mcg/ml in a 5%
solution

IG Prescribed for Diverse Infectious, Autoimmune Diseases

Primary humoral immunodeficiency disorders

Autoimmune neuropathies

- Guillain-Barré syndrome
- Chronic inflammatory demyelinating polyneuropathy
- Multifocal motor neuropathy
- Relapsing-remitting multiple sclerosis

Neuromuscular junction defects

- Myasthenia gravis exacerbations (myasthenic crisis)
- Lambert-Eaton myasthenic syndrome

Autoimmune mucocutaneous blistering disorders

- Bullous pemphigoid
- Pemphigus vulgaris and pemphigus foliaceus
- Mucous membrane pemphigoid
- Epidermolysis bullosa acquisita
- Stevens-Johnson syndrome/toxic epidermal necrolysis

Autoimmune inflammatory disorders

- Kawasaki disease
- Dermatomyositis
- Polymyositis
- Stiff person syndrome

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Hematological disorders

- Immune thrombocytopenic purpura
- Neonatal alloimmune thrombocytopenia
- Post-allogeneic bone marrow transplant setting
- B cell chronic lymphocytic leukemia
- Warm antibody autoimmune hemolytic anemia
- Anti-phospholipid syndrome

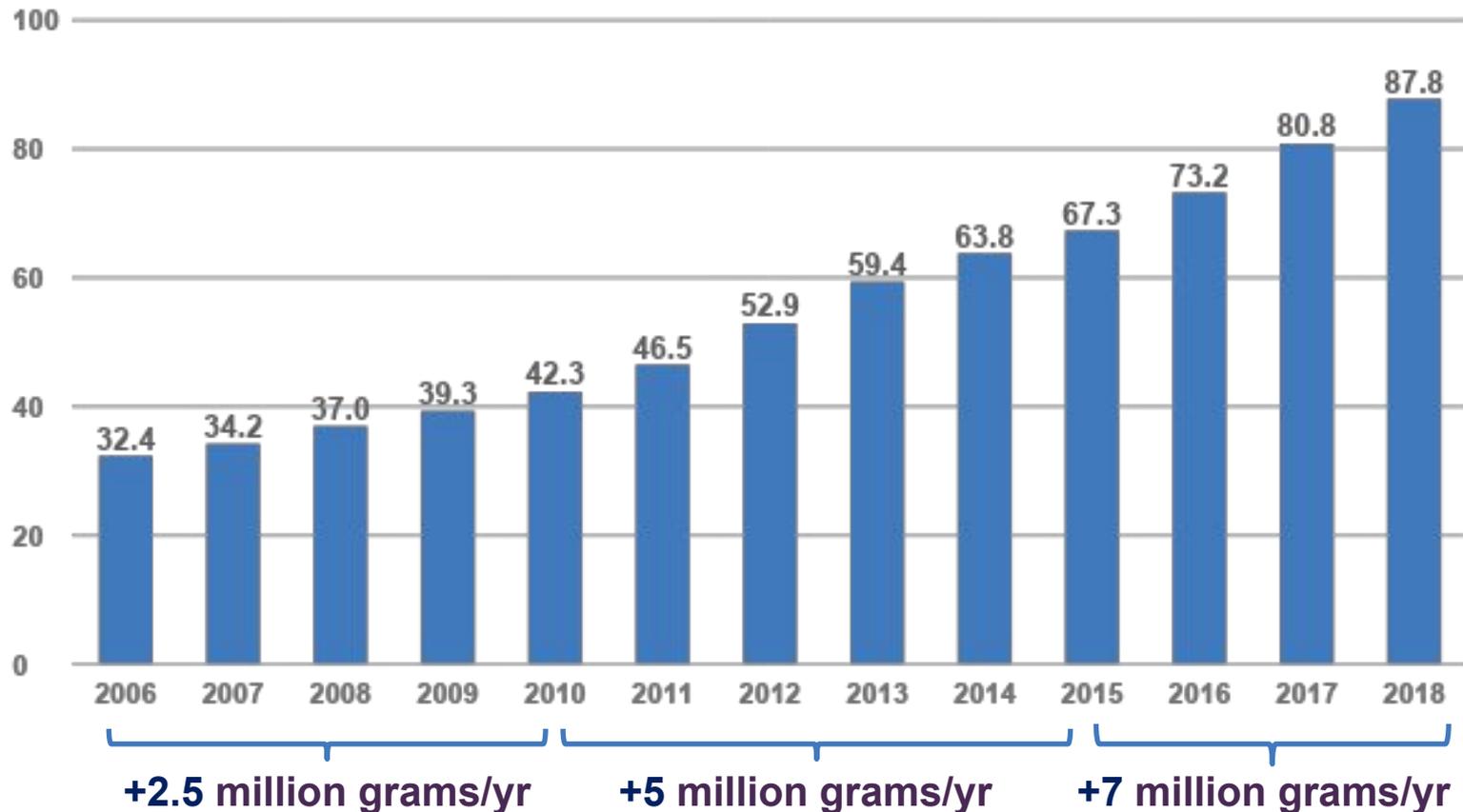
Infectious diseases

- Toxic shock syndrome
- Pediatric HIV infection (prevention of bacterial infection)

Solid organ transplantation

- Densitization of pre-renal transplant ABO incompatibility
- Acute humoral rejection of kidney allograft
- Cytomegalovirus-induced pneumonitis

U.S. IG Market: Growth Accelerates Over Last 12 Years



A photograph showing a young girl in a pink shirt and her mother in a grey cardigan smiling and interacting with a doctor in a white lab coat. The doctor is seen from the side, reaching out with his hand. The background is a bright, blurred indoor setting, possibly a home or a clinic.

FOUNDED IN 1988

We go beyond distribution because
the *patients are always first.*

"At the end of every transaction, there's a patient waiting for that product."

- Patrick M. Schmidt, Chief Executive Officer

Premier Specialty Distributor – FFF Enterprises

Specialty
Products

Flu
Vaccine
Program

Plasma /
IVIG/Albumin
& other
therapies



Biosimilars

Drug
Shortage
ProvideGX



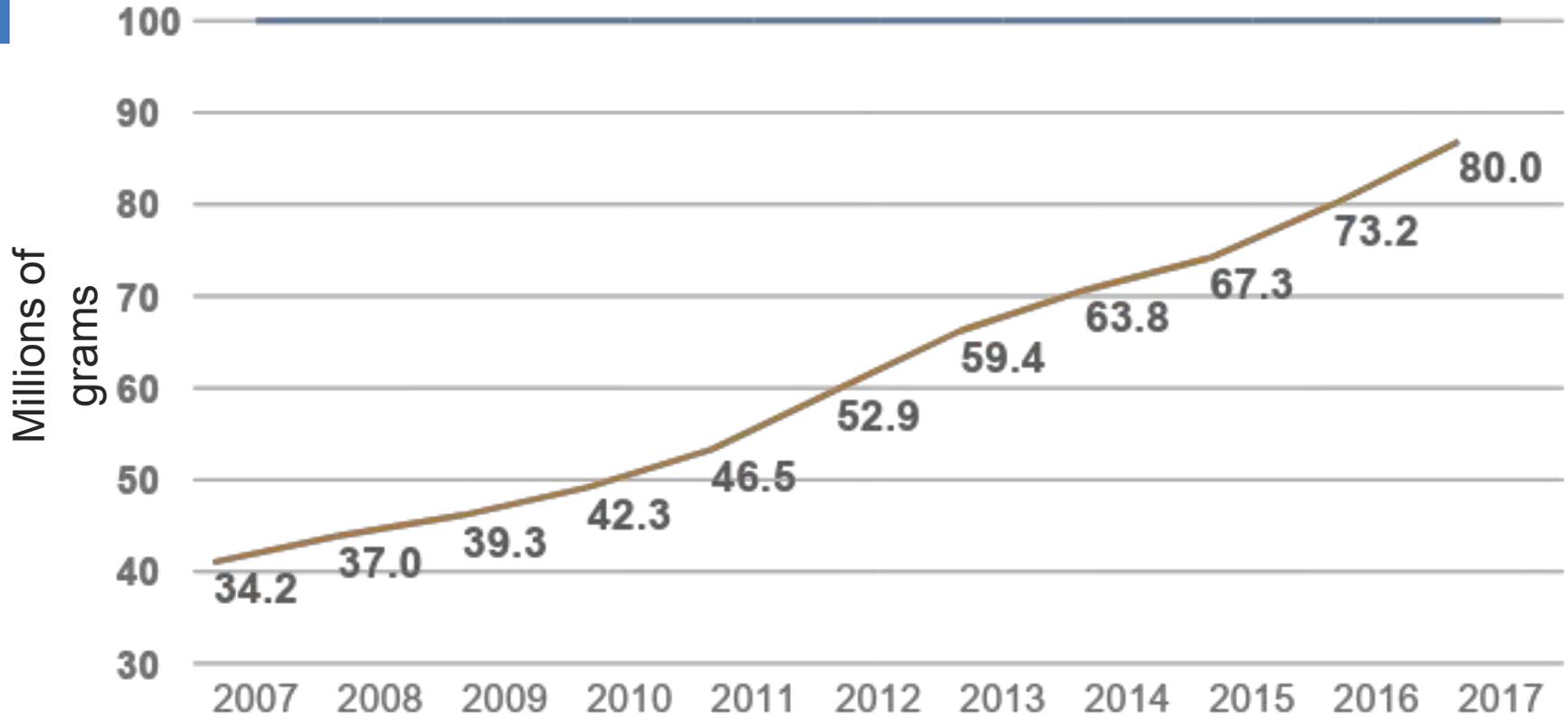
Premier
Unit Dose
Program

Existing Structures Used to Manage the IVIG Supply

Patrick M. Schmidt, Chief Executive Officer,
FFF Enterprises, Inc.

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The \$7 Billion U.S. Ig Market Continues to Grow About 8% Annually; Ig Demand Reached 80 Million Grams in 2017



IVIG ASP by Year

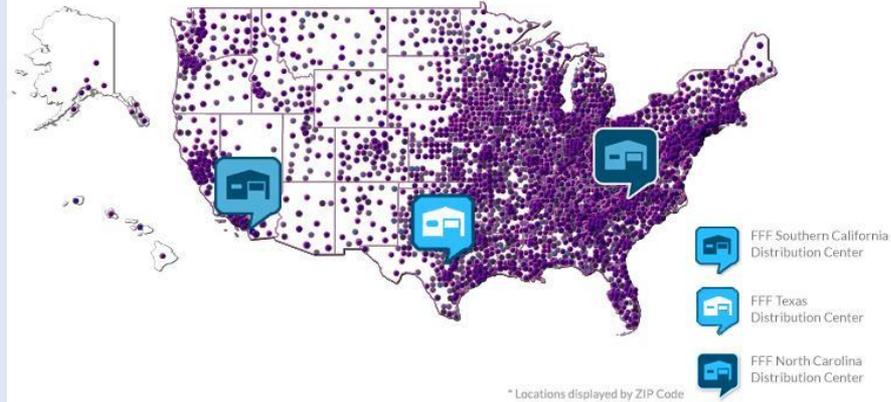
| Year | IVIG ASP |
|----------|----------|
| 2016 | \$72.10 |
| 2017 | \$73.04 |
| 2018 | \$76.39 |
| 2019 | \$81.38 |
| 2020 YTD | \$83.94 |

(After Discounts)

**Excluding 340B*

Specialties and Healthcare Providers We Service

- Allergy/Immunology
- Clinics and Multi-Specialty
- Dental
- Dermatology
- Dialysis
- Endocrinology
- Family Practice/General Practice
- Gastroenterology
- Health Departments
- Hematology/Oncology
- Hospital Based
- Infectious Disease
- Internal Medicine
- Neurology
- OB/GYN
- Ophthalmology
- Pediatrics
- Pulmonary
- Rehabilitation
- Rheumatology
- Vein Clinics



- Established accounts representing 96% of U.S. hospitals
- Strong physician presence with 74,000 accounts across numerous specialty groups
- Retail pharmacy accounts totaling over 25,000
- Accounts established with approximately 60% of home infusion providers
- Proven experience in expanding to new sites of care
- Payer contracts with PBMs, HMOs, PPOs, TPAs covering more than 160 million lives

Octapharma USA Extends Funding for COVID-19 Study Following Positive Preliminary Research Data

Study in California Utilizing IVIG as Investigational Coronavirus Treatment for Adults Experiencing Respiratory Failure

June 03, 2020 08:00 AM Eastern Daylight Time

PARAMUS, N.J.--(BUSINESS WIRE)--Following positive preliminary data, Octapharma USA is extending funding for an investigator-initiated study (IIS) focused on treating the most critical patients at the heart of the coronavirus pandemic, those experiencing hypoxia and who are at the highest risk of requiring mechanical ventilation. The research is led by infectious disease clinician George Sakoulas, M.D. of Sharp Memorial Hospital and the Sharp Rees-Stealy Medical Group in San Diego, Calif., and Associate Professor in the Department of Pediatrics of the University of California San Diego School of Medicine.

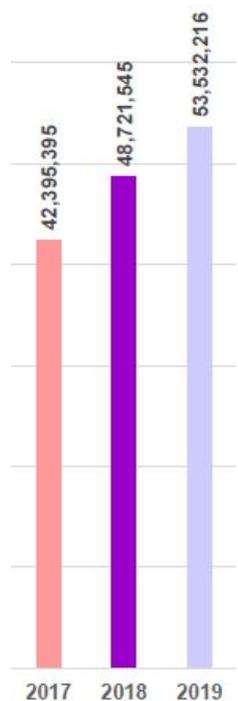
The randomized open label study is evaluating the standard of care (SOC) plus intravenous immunoglobulin (IVIG) compared to SOC alone in the treatment of COVID-19 infection, specifically in preventing mechanical ventilation in COVID-19 patients requiring high-flow oxygen. “Most of the morbidity and mortality in COVID-19 patients, as well as the burden on healthcare resources, follows the need for mechanical ventilation,” said Dr. Sakoulas. “If you can prevent the need for ventilation, the disease becomes much easier to manage at many levels.”

Dr. Sakoulas originally planned to enroll 20 patients in the study and has currently enrolled 27 adult patients. Patients are randomized into the two groups. To date the study has observed:

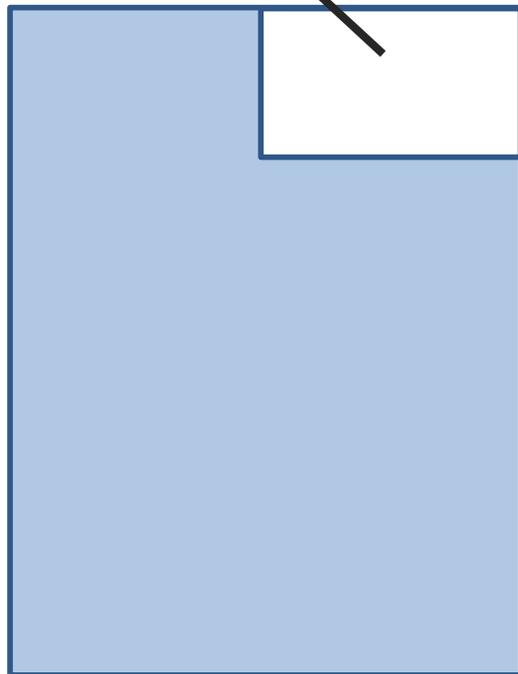
- Six patients in the SOC arm and two patients in the IVIG arm required intubation.
- Fourteen cumulative ventilator-dependent patient days among the total of 14 IVIG arm patients, as compared to a cumulative 74 ventilator-dependent patient days from the 13 patients in the SOC arm.
- All of the first five patients enrolled in the IVIG arm during the first week of May have been discharged home and are breathing independently on room air.
- Of the first five patients enrolled in the SOC arm, one has died, one has been discharged home, one remains ventilator dependent, and two are hospitalized on a medical floor.

Estimated 2019 IVIG/SCIG Production Loss Assuming COVID-19 Pandemic Reduces U.S. Source Plasma Collections by 10%

53.5 million U.S. source plasma collections in 2019*



COVID-19 pandemic reduces collections by 10% (5.35 million)



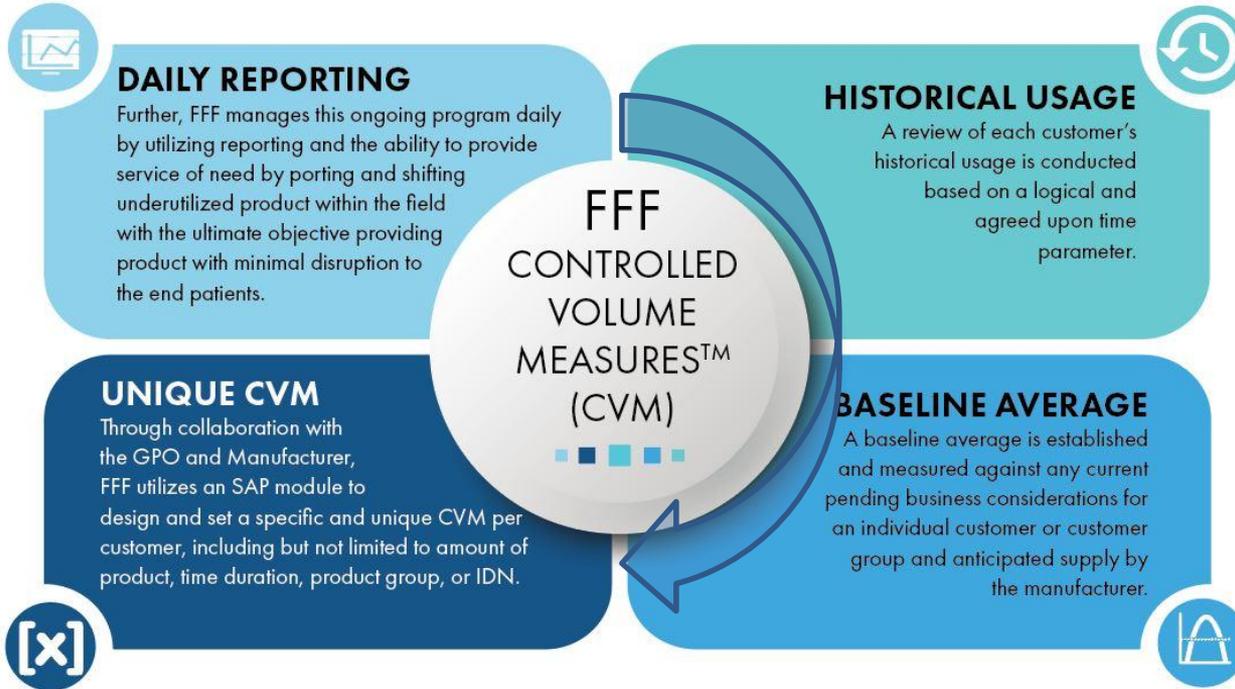
At ~800 mL per average collection, translates into loss of **4.3 million liters of plasma**

At ~4 grams/liter, translates into loss of **17 million grams of IgG for IVIG/SCIG products**

*Source: Plasma Protein Therapeutics Association

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FFF's Allocation Model



Controlled Volume Measures™ (CVM) – In times of **market shortage or product supply constraints**, FFF has the ability and flexibility to manage products through CVM's.

Supply Chain Investments

VIPc



MinibarRx



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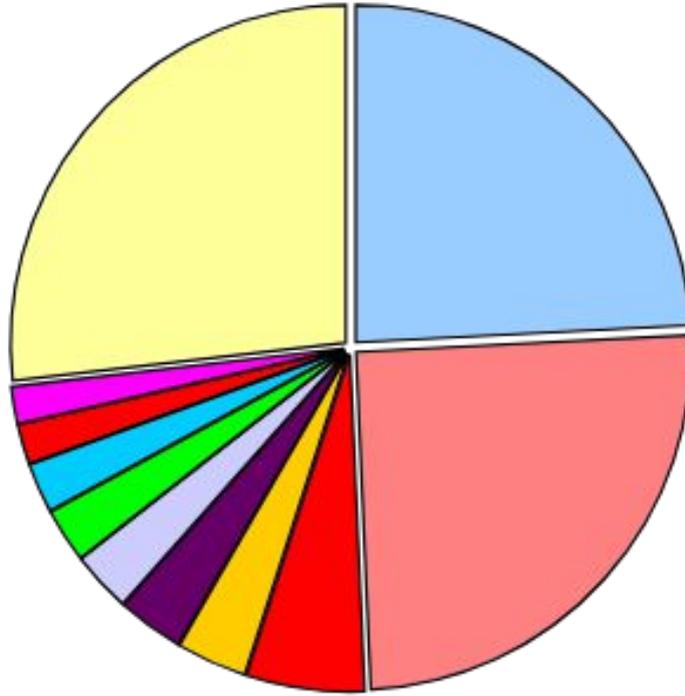
**One Rare Autoimmune Neuromuscular Disorder –
Chronic Inflammatory Demyelinating Polyneuropathy
(CIDP) – Accounts for One-Quarter of
Immunoglobulin Utilization
in the United States:
Taking a Closer Look**

2020

INCIRCLE LLC
Temecula, CA

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CIDP Accounts for an Estimated 24% of the U.S. IVIg/SCIg (Ig) Market



2017 Ig market: **80 million grams**

CIDP share: **19.2 million grams**

CIDP Ig cost: \$1.7 billion*

*Estimate based on sales volume weight-averaged Medicare payment rates for the 3 leading Ig products (\$88/gram). Does not include clinic/home-based Ig infusion costs.

Source: The Marketing Research Bureau, Inc. (Orange, CT)

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Expert Review of 65 Patients Previously Diagnosed With CIDP by Community Neurologists and Referred for Home IVIg Therapy¹

- Review of clinical and electrophysiologic (EP) data for 65 consecutive patients treated with IVIg for CIDP diagnosed with CIDP²
- 3 neuromuscular specialists independently applied EFNS/PNS criteria to classify “CIDP” cases: (1) **fulfills CIDP criteria**; (2) **non-CIDP** (neither clinical nor EP criteria met); or (3) **unknown** (insufficient information)
- **Only 7 patients (11%) met both clinical and electrodiagnostic CIDP criteria.**
The remainder did not have CIDP (49%) or were unknown (40%).

The investigators concluded that “adherence to EFNS/PNS CIDP diagnostic and treatment guidelines in the general neurologic community was poor.”

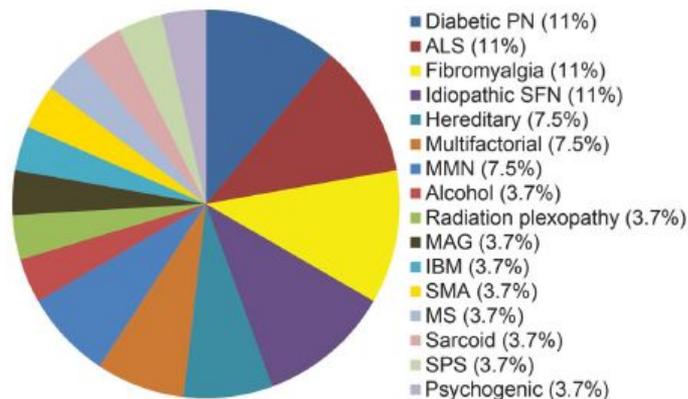
¹Allen JA, Gorson KC and Gelinas D. Challenges in the diagnosis of chronic inflammatory demyelinating polyneuropathy. *Brain Behav* 2018 Mar;8:e00932.

²Patients were diagnosed with CIDP by 31 community neurologists in 14 states

Nearly One-Half of Patients Referred to Academic Neuromuscular Practice with Diagnosis of CIDP Failed to Meet Diagnostic Requirements*

- Retrospective study of **59 consecutive patients referred to Northwestern University with a diagnosis of CIDP**
- **47% of patients were misdiagnosed** (figure →)
- None of 27 misdiagnosed patients met EFNS/PNS clinical criteria
- Original electrodiagnostic studies often misinterpreted or technically inadequate: **just 11% met definite EFNS/PNS CIDP criteria**

Alternative Diagnosis for Patients Without CIDP



ALS = amyotrophic lateral sclerosis; IBM = inclusion body myositis; MAG = myelin-associated glycoprotein; MMN = multifocal motor neuropathy; MS = multiple sclerosis; PN = polyneuropathy; SFN = small fiber neuropathy; SMA = spinal muscular atrophy; SPS = stiff person syndrome.

*Allen JA, and Lewis RA. CIDP diagnostic pitfalls and perception of treatment benefit. *Neurology* 2015;85:498-504.

INSIGHTS Study: Expert Review of 248 Presumptive CIDP and MMN Patients Referred by Community Neurologists for Initial Home IVIg Therapy*

- 8 neuromuscular clinicians independently reviewed all written notes, lab data, imaging reports and electrodiagnostic studies supplied to insurance companies to secure IVIg coverage approval for 248 patients
- Patients were referred for IVIg therapy by 154 physicians in 26 states
- **Only 32% of patients were determined to have an immune neuropathy**; Nearly one-half (46%) had neuropathies that were clearly not immune-mediated
- Only 15% met electrodiagnostic criteria for a demyelinating neuropathy
- Reviewers determined that **only 37% of cases with follow-up records responded to IVIg therapy**

*Levine TD, Katz JS, Barohn R, et al. The neuropathy review process for IVIg treatment: lessons learned from the INSIGHTS study. *Neurol Clin Pract* (in press).

INSIGHTS Study – Largest Review of Immunoglobulin Specialty Drug Therapy (IVIg) Utilizat



Date

- Review of 248 patient progress notes, lab data, and electrodiagnostic studies supplied to insurance companies for IVIg in neuropathy
- Referred for IVIg therapy by 154 physicians in 26 states
- **ONLY 32%** of patients receiving treatment were determined to have an immune neuropathy
- Half diagnosed with neuropathies that were clearly **not immune-mediated**
- Only 15% clearly met electrodiagnostic criteria for a demyelinating neuropathy



- **Other studies have shown similar results** *Levine TD, Katz JS, Barohn R, et al. The neuropathy review process for IVIg treatment: lessons learned from the INSIGHTS study. *Neurol Clin Pract* (in press).

Ig Therapy May Be Prescribed Each Year to as Many as 13,000 Patients Diagnosed With CIDP, But Who Don't Have CIDP or an Immune Neuropathy

Highest reported CIDP prevalence in large population applying EFNS/PNS criteria^{1****}

4.6 per 100,000



2017 CIDP Prevalence

15,600

2017 U.S. Ig Utilization Specifically for "CIDP"²

24% x 80 million total IVIg/SCIg grams

19.2 million grams

Less 30% who are **untreated**³ and conservatively 20% on **non-Ig immunotherapy**⁴

<7,800>

Estimated Average Annualized Ig Use Per Diagnosed "CIDP" Patient⁵

910 grams

Estimated actual CIDP Patients on Ig Therapy in 2017

7,800

Estimated number of presumptive "CIDP" patients receiving Ig therapy in 2017

21,000

13,200

¹Rajabally YA et al. *Muscle Nerve* 2009;39:432-8. ©The Marketing Research Bureau, Inc. (Orange, CT)

³Gorson KC et al. *J Periph Nerv Syst* 2010;15:326-33. **31%** of 106 consensus cases of CIDP were not receiving treatment. Also, among all 46 affirmed CIDP cases in a UK study (Rajabally 2009), **43.5%** did not require immunomodulatory therapy as a consequence of "clinical stability, spontaneous remission or mild disease."

⁴2010 GBS/CIDP International patient survey (n=858): 58% of treated patients reported they were on Ig therapy, 18% on steroids, 24% on other immunotherapies. In 2017 70% of treated patients assumed to be on Ig therapy. Per 100 CIDP patients, 70 are on treatment; of those 70, $0.7 \times 70 = 50$ are on Ig therapy, leaving $0.3 \times 70 = 20$ patients on other immunotherapies.

⁵IVIg and SCIG Utilization in the Atlantic Provinces 2016/17. In fiscal year 2016/17, 102 patients in the four eastern Canadian provinces received 92,968 grams of IVIg and SCIG.



- ✓ **FIRST to Market** Technology Solution that Facilitates Standardized Decision Making for Specialty Drugs
- ✓ Based on Groundbreaking Insight Study
- ✓ Algorithmically Enabled So the Right Patient Gets the Right Drug
- ✓ Saves Unnecessary Treatment for Patients and Costs For The Payor and Educates Provider.

InCircle is Powered by NuFactor and FFF Enterprises

- Novel opportunity to improve the management of costly specialty drugs like IG.
- Allows providers, specialty pharmacies and payors to work together.
- Deliver the right drug to the right patient, reducing costs and improving outcomes.
- Algorithmic solution combines the ***knowledge of key opinion medical experts*** with ***necessary data to make accurate diagnostic decisions***. The program is poised to benefit all key stakeholders by:
 - ✓ Ensuring providers submit key data in a uniform, standard format
 - ✓ Aligning care needed to the data reviewed
 - ✓ Providing standardized dosing and tapering practices
 - ✓ Improving communication with prescribers to monitor response to therapy in diagnostically questionable cases and educating prescribers along the way
 - ✓ Giving the payor a transparent and consistent view of the decision-making process

What does InCircle* Provide?



Data extractors



Proprietary computer
algorithm



Expertise in
neuromuscular
disease



Standardized data
collection



One-page case
summary



Prescriber education
unique to each case



**Improved patient
outcomes**



**Decrease Drug
Spend and Related
Costs for All**

*Powered by NuFactor and FFF Enterprises

We can optimize the available Ig supply by:

- Work Together & Stick Together
- Consider SCIG where and when appropriate
- Make sure CIPD is CIDP –InCircle Review Process
- Consider FDI VIPc Managed Ig Auto-Replenishment
- Unmet need for IM-Covid19-Ig?

Resources on IVIG Stewardship/Conservation Strategies

Sudha Narayanaswamy, Vice President, Pharmacy Practice,
Acurity Inc.

[Am J Health Syst Pharm.](#) 2019 Nov 13;76(Supplement_4):S102-S106.

Optimization of intravenous immune globulin use at a comprehensive cancer center.

[Figgins BS](#)¹, [Aitken SL](#)¹, [Whited LK](#)¹.

Division of Pharmacy, The University of Texas MD Anderson Cancer Center, Houston, TX.

PURPOSE:

Intravenous immune globulin (IVIG) is a high-cost medication used in a diverse range of settings. At many institutions, IVIG is dosed using total body weight (TBW). Recent evidence suggests that alternative dosing weights reduce waste without compromising clinical outcomes. The objective of this study was to quantify the waste reduction potential generated through the use of alternative IVIG dosing weights.

METHODS:

We performed a retrospective analysis of all IVIG doses administered from January 2011 through January 2016 to adults (≥ 18 years). TBW and height at the time of administration were used to calculate prescribed dose (g/kg), ideal body weight (IBW), and adjusted body weight (AdjBW). Three dosing methods were analyzed, as follows: use of AdjBW if TBW is $>120\%$ IBW (method 1), AdjBW for all doses (method 2), and IBW for all doses (method 3). Outcomes included potential IVIG use averted, direct drug cost savings, and reductions in outpatient infusion times for each method.

[Am J Health Syst Pharm](#). 2019 Nov 13;76(Supplement_4):S102-S106.

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RESULTS:

A total of 9,918 doses were administered to 2,564 patients over 5 years, representing an average usage of 75,994 g/year. If dosing methods 1, 2, and 3 had been used, the annual use of IVIG would have decreased by 21.9% (16,658 g/year, $p < 0.001$), 24.2% (18,371 g/year, $p < 0.001$), and 35.9% (27,252 g/year, $p < 0.001$), respectively. This translates into average annual cost differences of \$2.37 million, \$2.62 million, and \$3.89 million and average annual outpatient infusion time savings of 841 hours, 920 hours, and 1,366 hours, respectively.

CONCLUSION:

IVIG dosing optimization through use of alternative dosing weights represents a significant source of waste reduction and cost reduction.

Conservation Considerations

- **IVIG Stewardship**
 - Institution-specific guideline
 - Committee-based review/triage for inpatient/outpatient use
 - Pharmacist-driven stewardship
 - Dosing based on LBW or Adj. BW for appropriate indications
 - Waste-minimization strategies
- In case of a true shortage, consider
 - IVIG Task Force (MD, RN, Rx supply chain/clinical rep, legal, ethics, quality)
 - Subcutaneous vs Intravenous
 - Brand flexibility as appropriate
 - Alternatives for diseases as available (e.g., multiple sclerosis)
 - Dosing lower and titrating up for new starts

IVIG indicates intravenous immunoglobulin.

Questions & Answers

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Thank you.

Jenna Mandel-Ricci

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