Safety and IVIG Product Differences

Erwin W. Gelfand, MD

National Jewish Medical and Research Center

Denver, CO

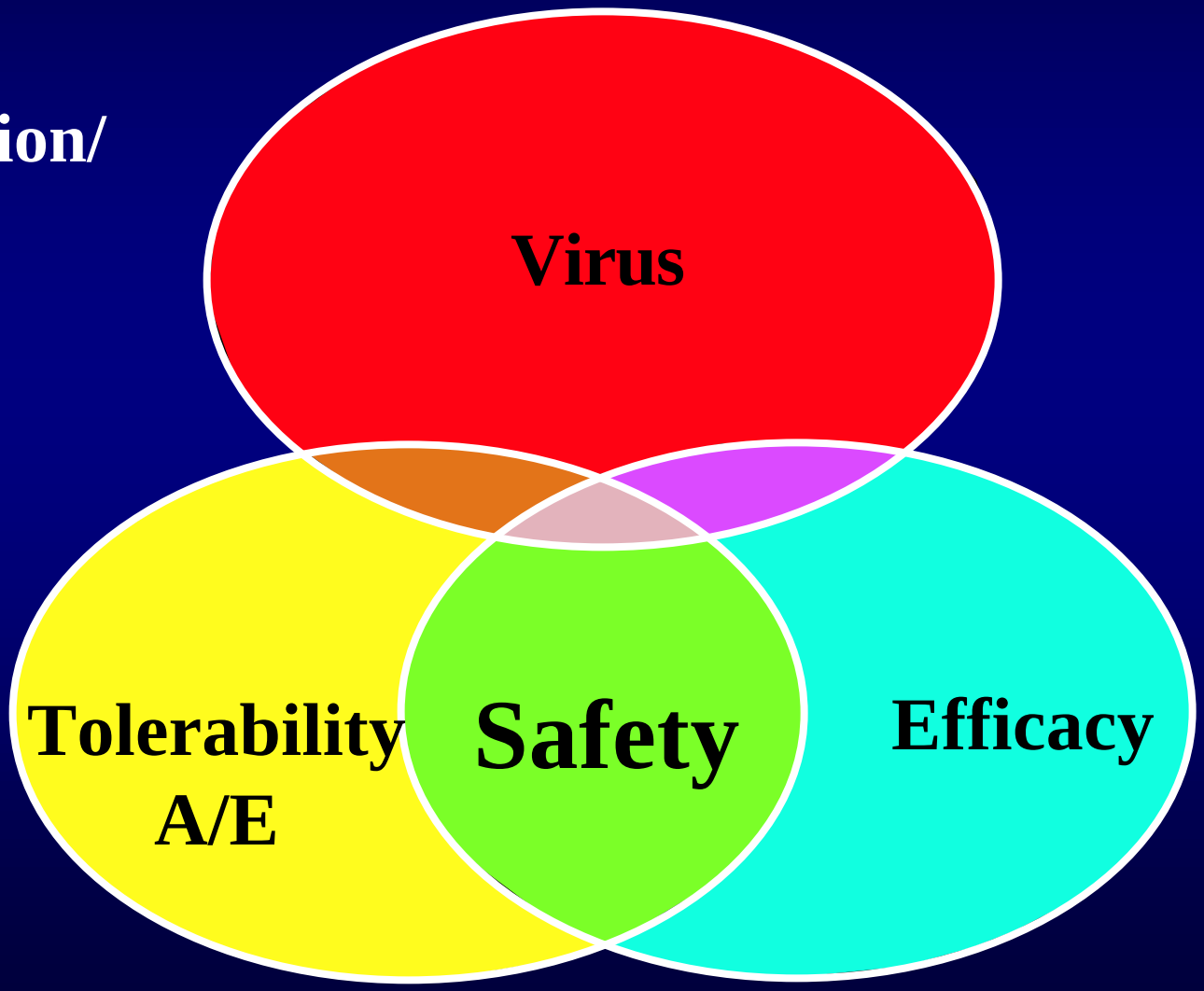
Comparison of Currently Available Products

Do the differences impact clinical outcomes?

Safety **A/E** **Tolerability** **Efficacy**

Comprehensive Approach to IVIG Safety

- Virus inactivation/ virus removal
- Tolerability
- Adverse events
- Efficacy



Advancements

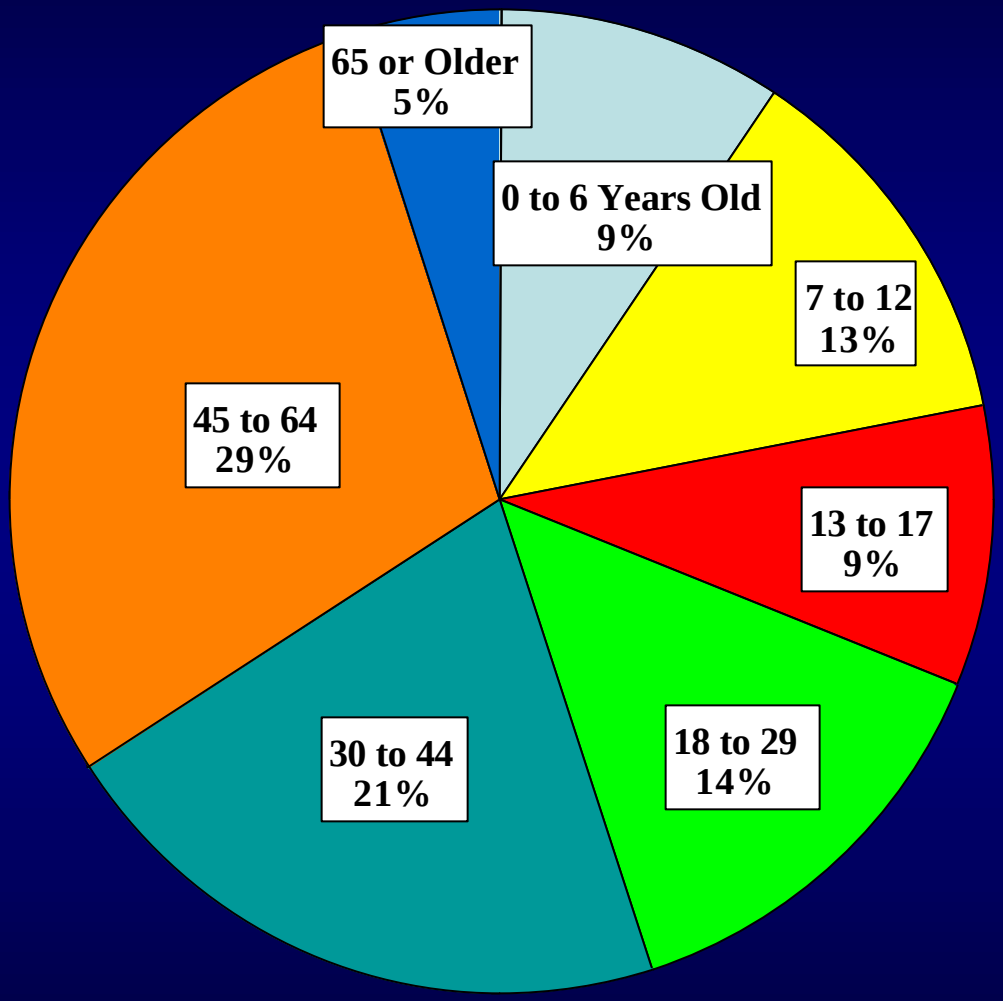
- In safety
  - Introduction of new standards
  - Complimentary methods
- In tolerability
  - More rapid infusions
- In incidence of adverse events
  - Low incidence in PID
  - No head-to-head comparisons
  - Different reporting methods
- In efficacy
  - Progressive improvement in infection prophylaxis

Evolution of Clinical Efficacy With Changes in Production of IVIG in PIDD

Product	Generation	Patients (n)	Infections* (#/year)
IGIM	1	13	3.54
Alkylated IGIV	2	14	1.24
Solvent/detergent-treated IGIV	3	73	0.43±0.88**
Caprylate/chromatography-treated IGIV	4	73	0.18±0.52**

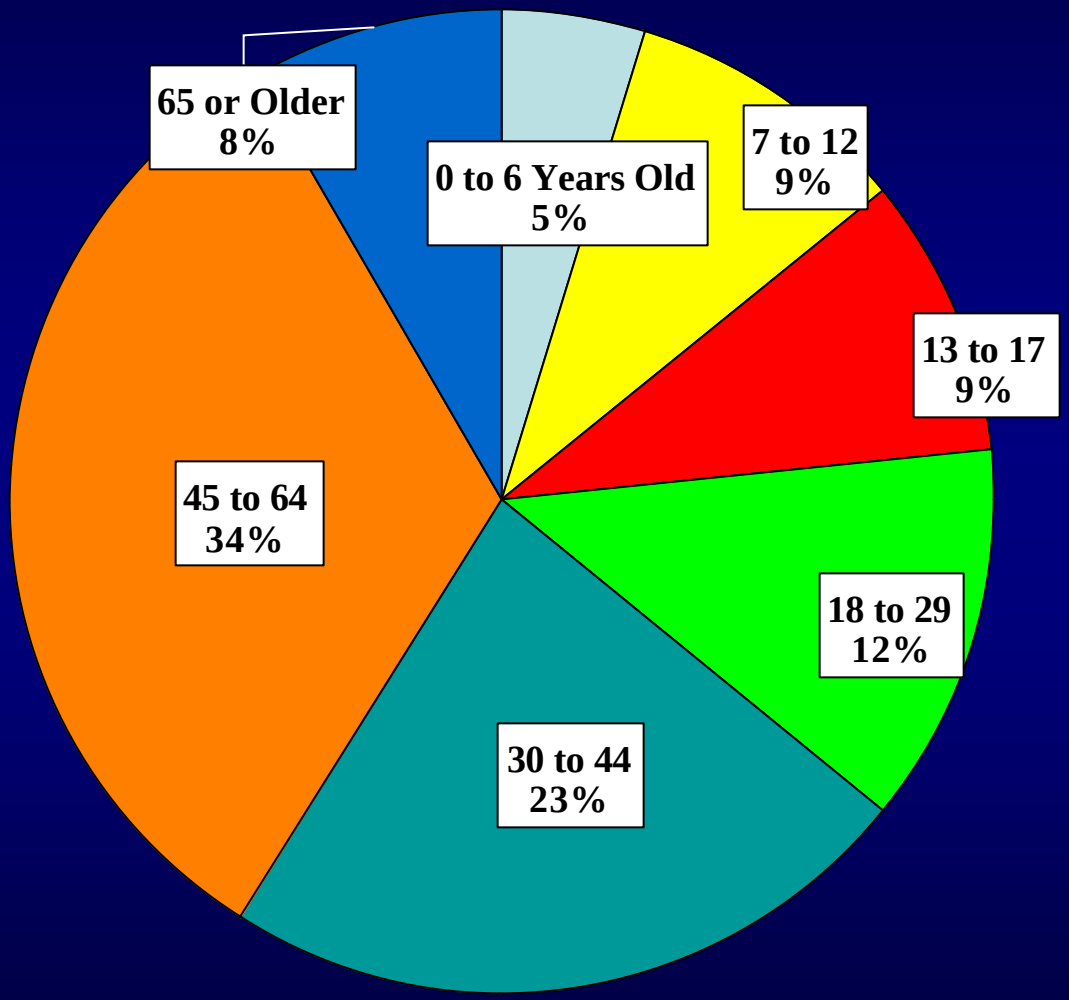
*Data are from independent studies using Bayer products and different doses
**Number of infections that were validated

Patients by Age



Q5. What is the date of birth of the (adult patient/oldest child) in the household with a primary immune deficiency disease? (Base: N=1,512 – excludes blanks)

Current IGIV Users by Age



Q2. What is the date of birth of the PID patient being treated with IGIV? N=1186

Challenges

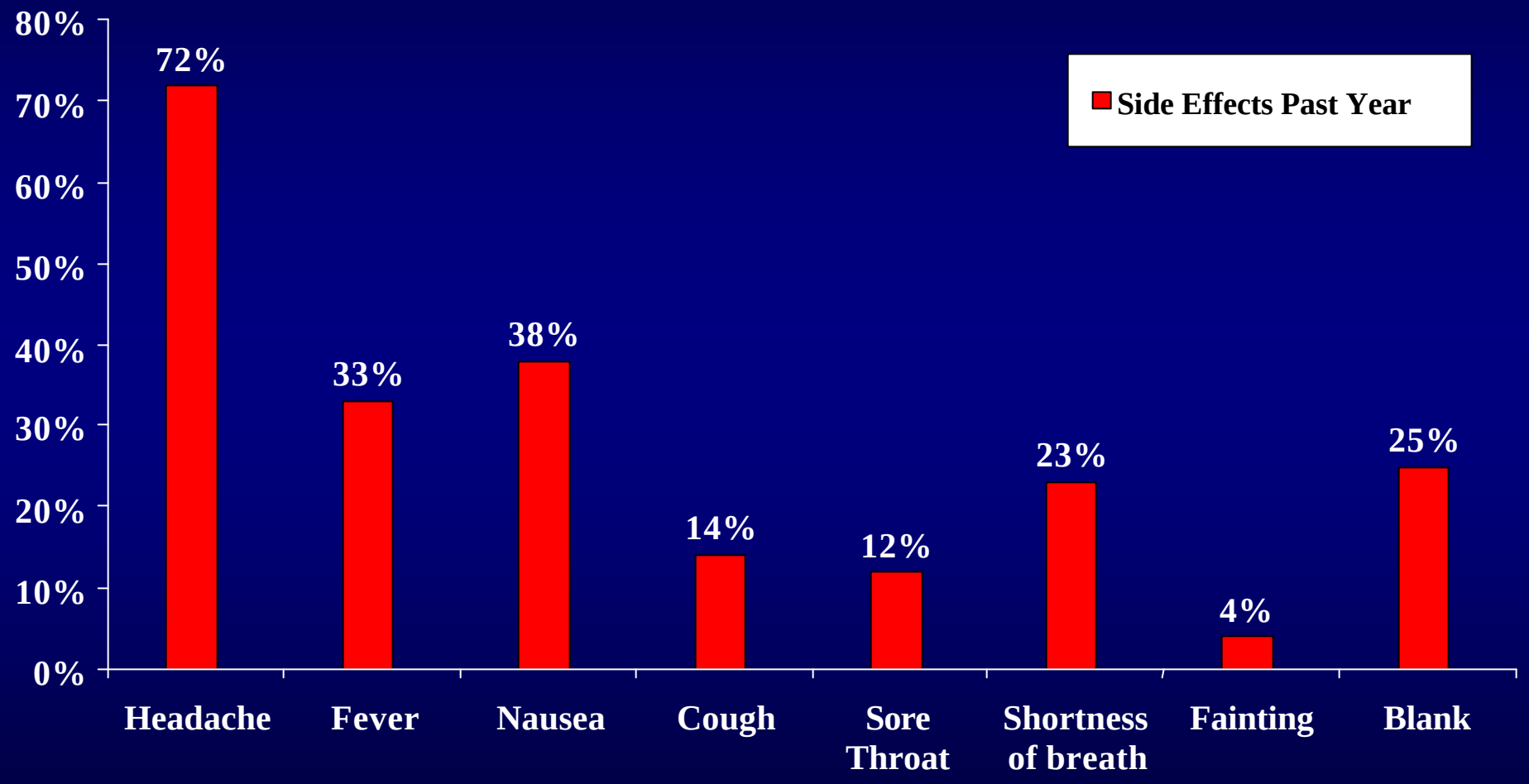
- The number of PID patients requiring Ig replacement has increased over the last decade

- The average age of patients receiving Ig replacement has increased dramatically

This poses additional new challenges in terms of safety:

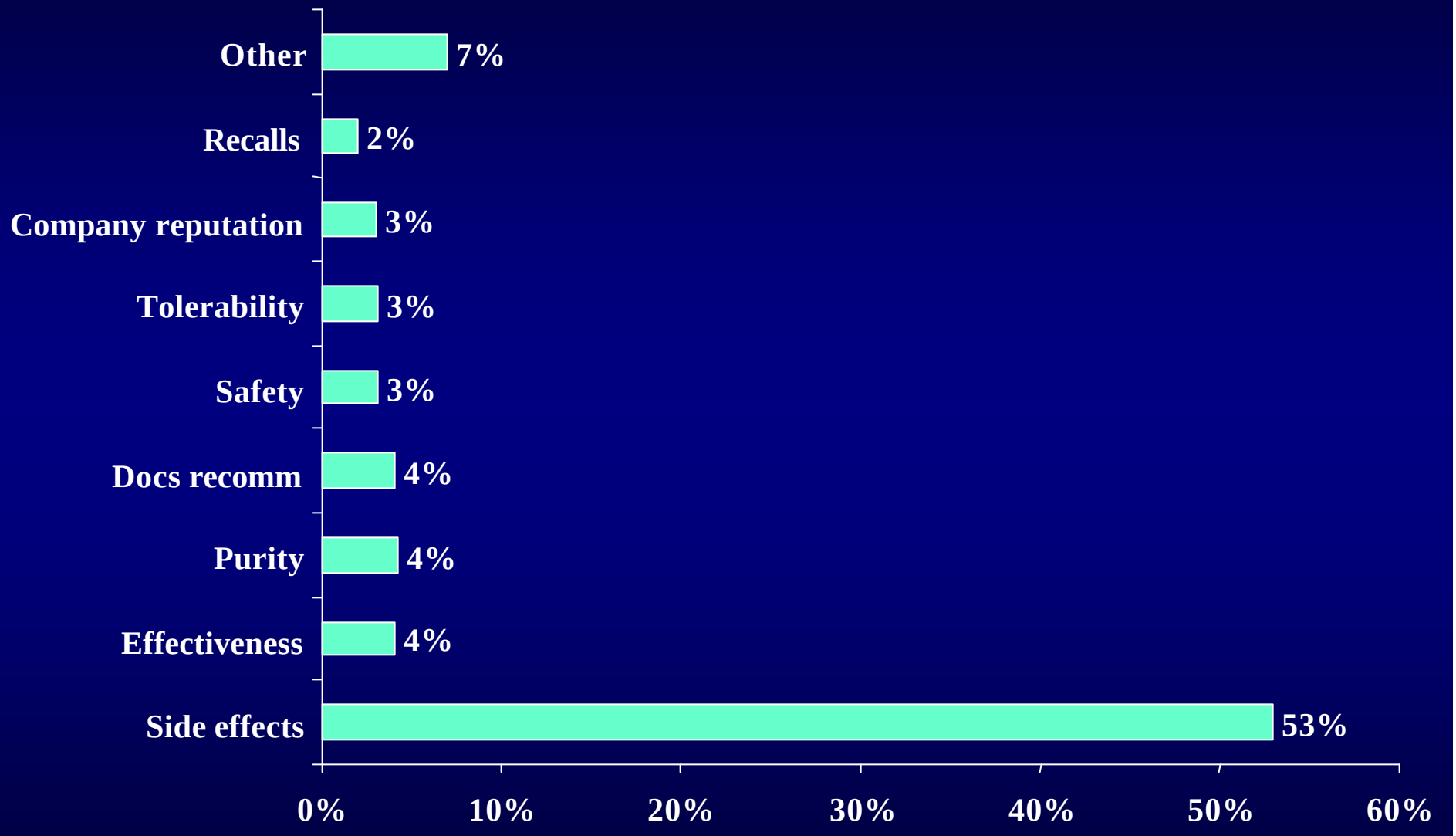
- Co-morbid diseases
- Fluid volume
- Salt load
- Sugar load
- Tolerability

Symptoms Following Infusion by Reported Side Effects in Past Year



Q40. During the past year, has he/she experienced any of the following after an IGIV infusion? N=1,186

Why Avoid Specific Products?



Q55c. Why do you try to avoid that/those product(s)? N=400

Limitations of Clinical Trial A/E Data

- Not head-to-head
  - Generally only when new product replaces old
- Study methodology differs
  - Recommendations change
  - Instructions to PI differ
- Patient selection not random
  - Many exclusions
- Few patients, many A/E; a lot a patients, few A/E

Incidence of A/E - Straight from the Package Insert

	Gamunex	Gammagard	Gammar - P IV	Venoglobulin
AE rate (overall)	42/825 inf = 5% This may b overestimate. Other PIs appea count an infusion once; ie if 2 AE one infusion then that infusion is for an AE and is counted as one	21/341 inf (6%) for 5% 23/219 inf (10.5%) sy for 10% sol and 35/21 (16%) local reaction fo sol	19 pt double blind c to Gammar-IV: 9/5 (16%) for Gamma comp to 13/52 inf (Gammar	20 pts, AE in 14.8% of the infusions. (8.9% chills, 7.6 pain, 3.8% headache).
Types of AE	pyrexia, rigors, dyspnea, cyan hypoxemia, bronchospasm, h dysfunction, leukopenia, pancyt tremor, erythema multiform epidermolysis, back pain, abdon pulmonary edema, seizures, hyp thrombosis	hypotension, headac chills, bachache, leg c lightheadedness, fev uticaria, flushing, elev pressure, nausau, vo may occur	chills, headache back/neck pain	Warning: Pts w/ aggamag extreme hypogammaglob É at risk of developing inflam reactions on infusion of Ver 10%. Reactions appear related to rate of infusionÉ temp, chills, nausea, von
AE	"No increase in creatinine and E observed"	"Increases in creatinir BUN have been obse	"Increases in creat and BUN have be observed"	"Increases in creatinine an have been observed", prog to oliguria or anuria, requ dialysis has been observ Severe renal AE "
Size of lice trials	3 randomized clinical trials: 1 double-blind, randomized, paral clinical trial; plus 2 PK trials 18 each; total of 119 subjects expo infusions with Gamunex.	17 pts/341 inf, no com or placebo, 5% solu	16-19 pts ? (only numbers mention 108 infusions	20 pts, 236 infusions

Product Features Affecting Clinical Tolerability and A/E

- Volume load (rate of infusion)
- Osmolality
- Sodium content
- Sugar content
- pH
- IgA content

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Shelf-Life	24 months	24 months	27 months		24 months	36 months	24 months	24 months	27 months		24 months
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Available Concentration	3-12%	5%	5%	10%	5%	10%	5%	3-12%	5%	10%	5%
Maximum Recommended Infusion Rate	>2.5 mL/kg/h	6 mL/kg/h	4 mL/kg/h	8 mL/kg/h	3.6 mL/kg/h	4.8 mL/kg/h	1.8 mL/kg/h	>2.5 mL/kg/h	4 mL/kg/h	8 mL/kg/h	4.2 mL/kg/h
Time to Infuse 35 gms *	<3.3 hrs (6% solution)	1.7 hrs	2.5 hrs	0.6 hrs	2.8 hrs	1.0 hrs	5.6 hrs	<3.3 hrs (6% solution)	2.5 hrs	0.6 hrs	2.4 hrs
Sugar Content	1.67 gm sucrose per gram of protein	50 mg/mL D-Sorbitol	20 mg/mL glucose	40 mg/mL glucose	50 mg/mL sucrose	None	50 mg/mL glucose	1.67 gm sucrose per gram of protein	20 mg/mL glucose	40 mg/mL glucose	100 mg/mL maltose
Sodium Content	<20 mg per gram of protein	<3.2 mEq/L	8.5 mg/mL	17 mg/mL	5 mg/mL	Trace amounts	3 mg/mL	<20 mg per gram of protein	8.5 mg/mL	17 mg/mL	1.75 mg/mL
Osmolarity/ Osmolality	192-1,074 mOsm/kg	240-350 mOsm/L	636 mOsm/L	1,250 mOsm/L	309 mOsm/L	258 mOsm/L	• 240 mOsm/L	192-1,074 mOsm/kg	636 mOsm/L	1,250 mOsm/L	310-380 mOsm/kg
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IgA content	720 mg/mL	<50 mg/mL	<2.2 mg/mL in a 5% solution		<25 mg/mL	46 mg/mL	<10 mg/mL	720 mg/mL	<2.2 mg/mL in a 5% solution		Š100 mg/mL

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Formulation	Lyophilized	Liquid	Lyophilized		Lyophilized	Liquid	Lyophilized	Lyophilized	Lyophilized		Liquid
Shelf-Life	24 months	24 months	27 months		24 months	36 months	24 months	24 months	27 months		24 months
Reconstitution Time	Several minutes	None (liquid solution)	<5 minutes at room temperature; >20 minutes if cold		<20 minutes	None (liquid solution)	Š10 minutes at room temperature	Several minutes	<5 minutes at room temperature; >20 minutes if cold		None (liquid solution)
Available Concentration	3-12%	5%	5%	10%	5%	10%	5%	3-12%	5%	10%	5%
Maximum Recommended Infusion Rate	>2.5 mL/kg/h	6 mL/kg/h	4 mL/kg/h	8 mL/kg/h	3.6 mL/kg/h	4.8 mL/kg/h	1.8 mL/kg/h	>2.5 mL/kg/h	4 mL/kg/h	8 mL/kg/h	4.2 mL/kg/h
Time to Infuse 35 gms *	<3.3 hrs (6% solution)	1.7 hrs	2.5 hrs	0.6 hrs	2.8 hrs	1.0 hrs	5.6 hrs	<3.3 hrs (6% solution)	2.5 hrs	0.6 hrs	2.4 hrs
Sugar Content	1.67 gm sucrose per gram of protein	50 mg/mL D-Sorbitol	20 mg/mL glucose	40 mg/mL glucose	50 mg/mL sucrose	None	50 mg/mL glucose	1.67 gm sucrose per gram of protein	20 mg/mL glucose	40 mg/mL glucose	100 mg/mL maltose
Sodium Content	<20 mg per gram of protein	<3.2 mEq/L	8.5 mg/mL	17 mg/mL	5 mg/mL	Trace amounts	3 mg/mL	<20 mg per gram of protein	8.5 mg/mL	17 mg/mL	1.75 mg/mL
Osmolarity/ Osmolality	192-1,074 mOsm/kg	240-350 mOsm/L	636 mOsm/L	1,250 mOsm/L	309 mOsm/L	258 mOsm/L	• 240 mOsm/L	192-1,074 mOsm/kg	636 mOsm/L	1,250 mOsm/L	310-380 mOsm/kg
pH	6.4-6.8	5.0-6.0	6.4-7.2		6.4-7.2	4.0-4.5	6.4-7.2	6.4-6.8	6.4-7.2		5.1-6.0
IgA content	720 mg/mL	<50 mg/mL	<2.2 mg/mL in a 5% solution		<25 mg/mL	46 mg/mL	<10 mg/mL	720 mg/mL	<2.2 mg/mL in a 5% solution		Š100 mg/mL

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Routes of Administration

I.V. vs Subcutaneous

Pros and Cons

Comparison of Routes of Administration

Subcutaneous

- Unsupervised
- Compliance not assured
- Irregular follow-up
- "Freedom"

Intravenous

- Supervised
- Compliance assured
- Regular follow-up
- "Group support"

Comparison of Routes of Administration

Subcutaneous	Intravenous
• Subcutaneous fat	• Venous access
• 4-6 hrs/week	• 1-1$^{1}/_{2}$ hrs/month
• Steady trough levels	• Peak-to-trough variability
Equal trough levels	
• Maximum volume at 1 site (2.5 ml/kg: 16.6%= 415 mg/kg, max 25 mls)	• No limit infusion
• Few (if any) systemic A/E	• Low incidence systemic A/E
• Local A/E	• No local A/E

Comparison of Routes of Administration

Subcutaneous

- Cost/gram
- Pump, equipment
- Teaching, reinforcement
- No nursing/facility charges

Intravenous

- Cost/gram
- Equipment available
- No teaching
- Nursing/facility charges

Not very different

Ideal IVIG

- Liquid, ready-to-use
- High concentration, 10%+
- Low incidence of A/E
- Good tolerability
- Efficacious

IVIG Administration

Old-Fashioned Way	Time		Modern Way
Patient arrives			Patient arrives
Pharmacy notified			
IVIG prepared	1 hr	15 min	IVIG prepared
IVIG delivered to infusion site			
i.v. started			i.v. started
Infusion			Infusion
3-5%	4.2 hrs	1.1 hrs	10%
0.04 ml/kg/min			0.08 ml/kg/min
120 mg/kg/hr			480 mg/kg/hr
8.4 gm/hr			33.6 gm/hr
	5.2 hrs	1.3 hrs	

Comparison of Routes of Administration

Subcutaneous	Intravenous
4-6 hrs/week	$1\text{-}1^{1}/_{2}$ hrs/month

Conclusions

- Ig replacement is a life-saving medication in patients with PID
- There have been significant advances in Ig replacement therapy
- Ig replacement is generally a safe mode of therapy - some concerns linger
- Patients now have options as to the route of administration. The subcutaneous option is currently not licensed, but under investigation