The Growing Domain of Intravenous Immunoglobulin

Dr Darryl Maher

CSL Limited

Bioplasma Division

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Outline

- Growth in demand for IVIG
- Why is it growing
  - the Interlaken Conference
- Some safety issues
- Meeting the growing demand
  - technology and yields
  - here in Asia

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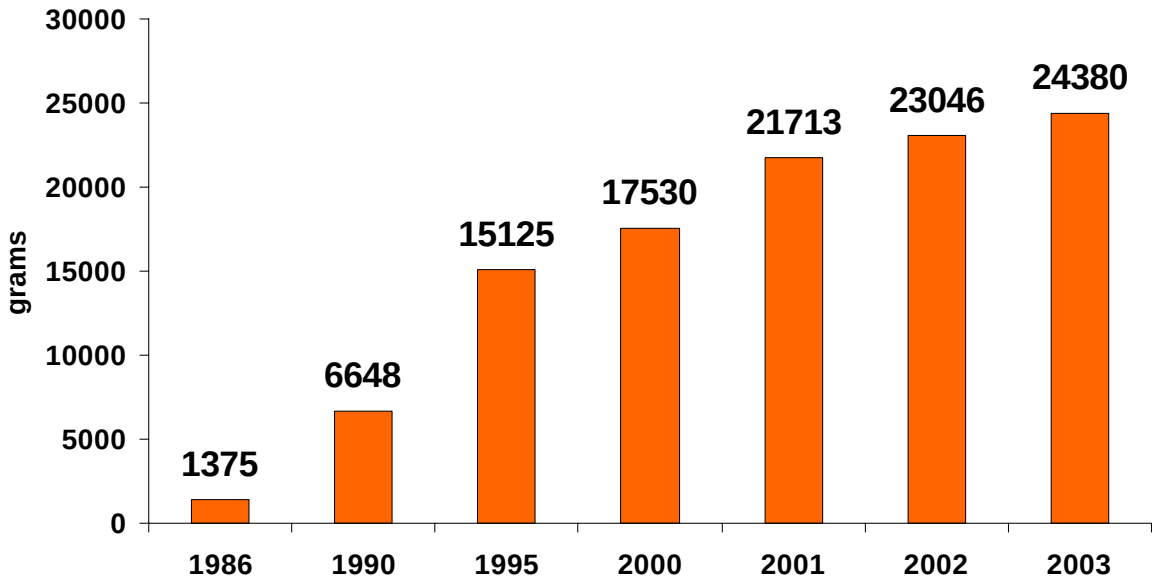
IVIG Volume in the USA



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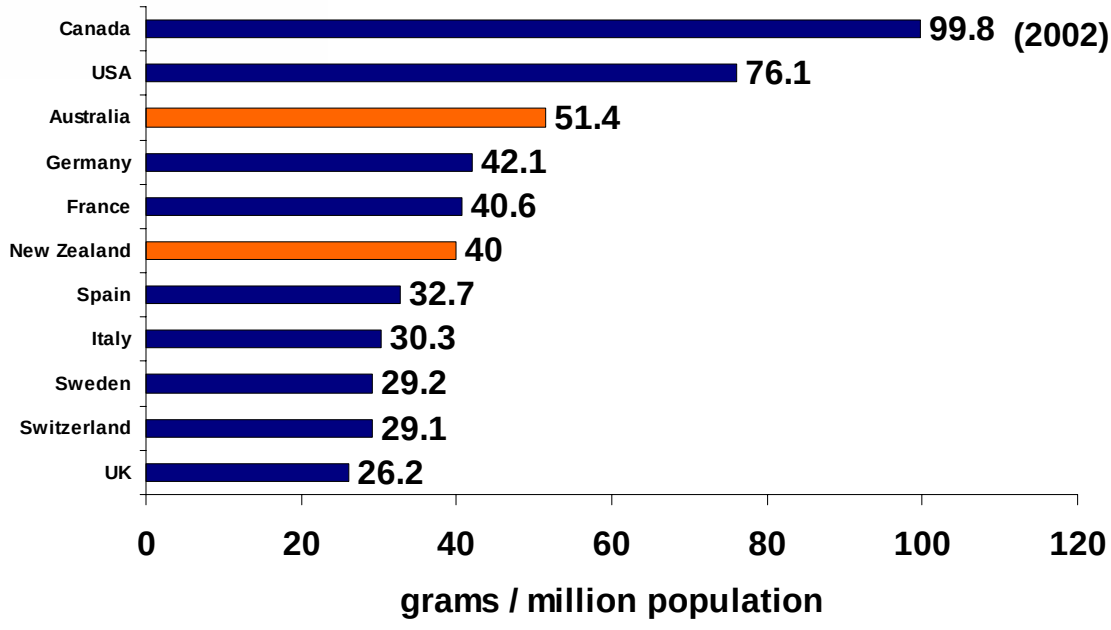
IVIG USAGE IN NORTH AMERICA / EUROPE 2001



The Marketing Research Bureau Inc (2002,2003)

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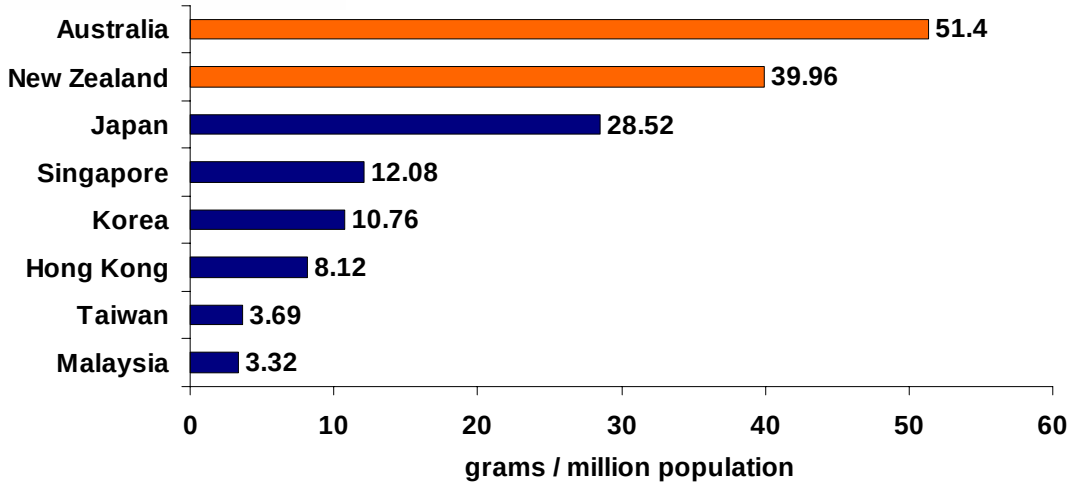
IVIG Usage in Asia (2000)



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Intragam P

Indications (Australia):

… replacement IgG therapy in

- primary immunodeficiency;
- myeloma and CLL with severe secondary hypogammaglobulinemia and recurrent infections;
- congenital acquired immune deficiency syndrome with recurrent infections.

… replacement immunomodulatory therapy in

- ITP in adults or children at high risk of bleeding or prior to surgery to correct the platelet count;
- allogeneic bone marrow transplantation;
- Kawasaki disease
- Guillain-Barre Syndrome

AHMAC Guidelines

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FDA approved indications for IVIG

- Primary agammaglobulinemia
- Common variable immunododeficiency
- X-linked agammaglobulinemia
- Severe combined immunodeficiency
- X-linked hyper-IgM deficiency
- IgG subclass deficiency
- Chronic lymphocytic leukemia
- Children with HIV
- Bone Marrow Transplantation (allogeneic)
- Idiopathic Thrombocytopenic Purpura
- Kawasaki syndrome

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Key Sessions

Molecular Aspects of Immunoglobulin Synthesis and Primary Immune Deficiencies

IVIG in Secondary Immune Deficiencies and Stem Cell Transplantation

The Use of IVIG in Dermatology and Allergy

Immunomodulation by IVIG

The Use of IVIG in Collagen Vascular Diseases, Vasculitides and Atherosclerosis

IVIG for Autoimmune Diseases of the Peripheral Nervous System

IVIG for Autoimmune Diseases of the Central Nervous System

Mechanisms of action of IVIG in autoimmune and inflammatory diseases

Michel Kazatchkine, Paris

- **Modulation of expression and function of Fc receptors**
- **Interference with activation of complement and the cytokine network**
- **Provision of anti-idiotypic antibodies**
- **Inhibition of maturation and function of dendritic cells**
- **Regulation of cell growth**
- **Effects on the activation, differentiation and effector functions of T and B cells**

Theoretical Mechanisms of Action of IVIG in Immune Thrombocytopenia

John Semple, Toronto

- **Competitive blockade of activating Fc receptors on macrophages**
- **Interactions with the inhibitory Fc gamma RIIB molecule**
- **Initiation of Fc gamma R mediated inhibitory cytokines**
- **Anti-idiotypic antibodies neutralising anti-platelet autoantibodies**

Reported uses of IVIG in Neurology

Marinos Dalakas, Bethesda

- **Neuropathies**
  - **Guillain Barre Syndrome**
  - **Chronic Inflamatory Demyelinating Polyradiculoneuropathy (CIDP)**
  - **Multifocal motor neuropathy**
  - **Diabetic neuropathy**
- **Neuromuscular disease**
  - **Myasthenia gravis**
  - **Eaton-Lambert Syndrome**
- **Inflammatory myopathies**
  - **Polymyositis / Dermatomyositis**
  - **Inclusion Body Myositis**
- **CNS diseases**
  - **Multiple Sclerosis**
  - **Stiff Person Syndrome**

IVIG for Guillain - Barre Syndrome

Pieter van Doorn, Rotterdam

- **Plasma exchange (PE) reduces time to walk by approximately 1 month**
- **PE, IVIG and PE plus IVIG all equivalent**
- **IVIG 0.4 g/kg for 6 days better than 3 days**
- **Recent Dutch randomised controlled trial N=225**

IVIG	IVIG + MP	
56%	68%	p=0.06

P = 0.01 after correction for prognostic factors

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Proven effective treatment for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

Treatment	*Cochrane review*	*Effect*	*Side-effects (potential)*	*Availability*	*Direct costs*
Prednisone	+	+	severe	very good	low
PE	-	+	minor	rather good	high
IVIG	+	+	minor / none	good	high

PE, Plasma exchange; IVIG, Intravenous immunoglobulin; +, positive

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IVIG in Relapsing - Remitting Multiple Sclerosis

P. S. Sorenson, Copenhagen

Study	Design	n	Age (years)	Duration of MS (years)	EDSS	IVIG Monthly (G/KG)	Trial duration (month)	Primary End - point
Fazekas et al	PG	150	37	7	3.3	0.2	24	EDSS changes
Achiron et al	PG	40	35	4	2.9	0.2	24	relapse rate
Sorensen et al	DC	26	35	5	3.5	2	6 x 2	MRI lesions
Lewanska et al	PG	49	38	8.5	3	0.2	12	relapse rate
							0.4	

PG, parallel groups; DC, double cross-over; EDSS,: MRI, magnetic resonance imaging

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Annual relapse rate (mean ± SD) in randomized trials of intravenous immunoglobulin (IVIG) in relapsing - remitting multiple sclerosis

Study	IVIG	Placebo	Effect size *	Weight *
Fazekas et al	0.52 ± 0.87	1.26 ± 2.2	-0.44	0.51
Achiron et al	0.59 ± 0.67	1.61 ± 0.98	-1.22	0.12
Sorensen et al ***	1.04 ± 1.74	1.80 ±3.14	-0.3	0.15
Lewanska et al				
0.2 g/kg	0.88 ± 1.26	1.24 ± 0.75	-0.35	0.12
0.4 g/kg	0.87 ± 0.99	1.24 ± 0.75	-0.43	0.11

Overall effect size * (95% confidence interval): -0.5 (-0.73 to -0.27), p = 0.00003

* Effect size: IVIG - placebo;

** proprotion of reciprocal of total variation attributable to given study

*** Extrapolated from 6 - month data

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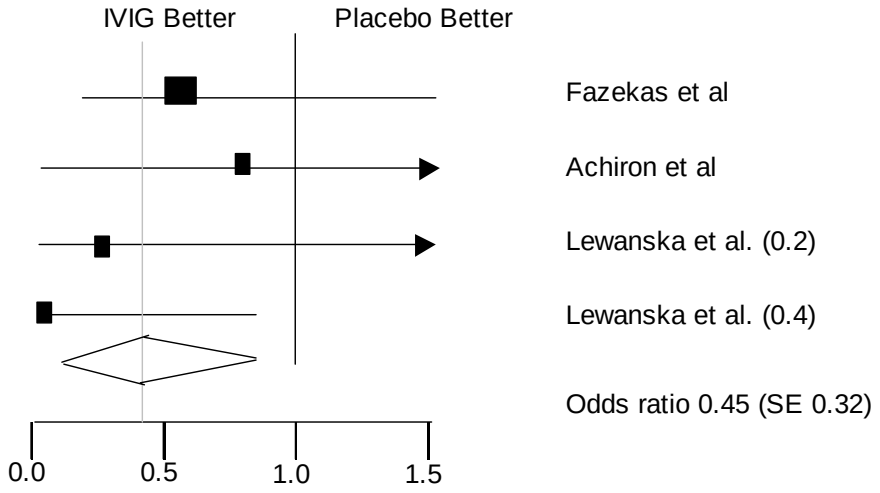
Odds ratios IVIG/placebo for deterioration in EDSS



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Stiffness scores in patients randomised to IVIG or placebo

Months	*Mean (95% CI)*	*Score Mean (95% CI)*	*p Value*
	Baseline *4.6 (3.4 - 5.7), n=7*	*Baseline* *4.7 (3.7 - 5.7), n=7*	0.85
	IVIG	***Placebo***	
1-2	3.8 (2.9 - 4.7), n=7	4.7 (3.7 - 5.7), n=7	0.21
2-3	3.0 (2.2 - 3.8), n=7	4.7 (3.8 - 5.6), n=7	0.02
3-4	3.0 (2.2 - 3.8), n=7	4.7 (3.7 - 5.7), n=7	0.02
	Washout	*Washout*	
4-5	3.0 (2.2 - 3.8), n=7	4.7 (3.7 - 5.7), n=7	0.02
	Placebo	*IVIG*	
5-6	3.7 (2.7 - 4.7), n=7	3.0 (2.3 - 3.7), n=6	0.30
6-7	4.0 (2.8 - 5.2), n=6	2.5 (2.1 - 2.9), n=6	0.05
7-8	4.0 (2.8 - 5.2), n=7	2.0 (1.5 - 2.5), n = 6	0.01

n, indicates number of patients with data collected at each visit; CI, confidence interval

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IVIG and Renal Transplantation
Denis Glotz, Paris

- Upto 30% of potential recipients have anti-HLA antibodies
  - lymphocytotoxic antibodies detected by cross match
- Strong correlation with severe acute rejection and graft loss
  - absolute contraindication to transplantation
- Patients can wait up to 3 years to find a compatible organ
- IVIG can block the cytotoxicity *in vitro*
  - anti-idiotypic antibodies
- Treatment with IVIG leads to prolonged decrease in anti-HLA titres

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IVIG and Renal Transplantation
Denis Glotz, Paris

- 15 patients with anti-HLA antibodies received IVIG
  - 87% responded and received a transplant within 4 months
  - 11/13 had successful grafts with no rejection at 18 months
- Jordan et al have described Randomised Study N=101

IVIG (n=49)	Albumin (n = 51)	
37%	17%	p<0.02

  - Transplanted within 1 year

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Interlaken Meeting - Dermatology

- **Striking and graphic session**
- **Dramatic responses in certain skin disorders especially autoimmune mucocutaneous blistering disorders**
- **Use in patients at severe end of the spectrum, failed conventional treatment or unacceptable side effects (high dose steroids, immunosuppresants)**

IVIG in Dermatology

- **Severe drug eruptions**
  - Stevens Johnson Syndrome
  - Toxic Epidermal Necrolysis
- **Bullous diseases**
  - Pemphigus
  - Bullous pemphigoid
  - Other
- **Dermatomyositis**
- **Intractable and severe forms of common skin disorders**
  - Atopic Dermatitis/Eczema
  - Psoriasis
  - Urticaria

IVIG in Dermatology - Issues

- Literature is limited - need for further studies
- Dose and frequency not well defined
- Long term follow up and safety studies
- Better understanding of mechanism of action
- Possibility of local infusion needs to be explored
- "Consensus statement on the Use of Intravenous Immunoglobulin Therapy in the Treatment of Autoimmune Mucocutaneous Blistering Diseases"

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TABLE III

PEMPHIGUS VULGARIS: Comparison of Treatment Outcomes Pre and Post IVIg Therapy

Clinical Variable	N	Average Prior To IVIg	Minimum	Maximum	Average After IVIg	Minimum	Maximum	Diff.	Sign Test P-Value	Sign Rank Test P-Value
Total Dose of Prednisone	20	35,202 mg	14,750 mg	89,500 mg	1,850 mg	1,180 mg	3,200 mg	33,352 mg	<.0001	<.0001
Duration of Prednisone Therapy	20	36.4 mo.	12 mo.	96 mo.	4.8 mo.	2.6 mo.	7.5 mo.	31.7 mo.	<.0001	<.0001
Duration of ISA Therapy	21	36.4 mo.	12 mo.	96 mo.	2.9 mo.	0 mo.	6 mo.	33.5 mo.	<.0001	<.0001
Side Effects	21	5.4	4	8	0.3	0	2	5.1	<.0001	<.0001
# of Hospital Admissions	21	3.1	1	8	0	0	0	3.1	<.0001	<.0001
Total # of days Hospitalized	21	30.3	9	108	0	0	0	30.3	<.0001	<.0001
Duration of Therapy	21	36.4	12 mo.	96 mo.	27.1 mo.	23 mo.	34 mo.	9.3 mo.	.66	.18
Relapses	21	7.9	0	18	1.2	0	5	6.7	<.0001	<.0001
Recurrences	21	5.6	2	12	2.7	0	6	2.9	.0007	.0003
Remissions	21	0	0	0	1	1	1	-	<.0001	<.001
Quality of Life	21	1.3	1	2	4.6	4	5	-3.3	<.0001	<.0001

Toxic Epidermal Necrolysis: Comparison of four studies available

	Viard et al 1998	Prins et al 2003	Trent et al 2000	Bachot et al 2000
Study Type	prospective, non-controlled	retrospective, non-controlled	retrospective, non-controlled	prospective, non-controlled
Number of Patients	10	48	16	34
Average age (years)	39	43	43	47
Average detachment (%)	28.5	45	43	19
Dose IVIG (total) (g/kg)	3	3	4	2
Predicted deaths	(30%)	(30%)	5.8 (36%)	8.2 (24%)
Actual deaths	0/10 (0%)	6/48 (12%)	1/16 (6%)	11/34 (32%)
Deaths from renal failure	0	0	0	6

IVIG, intravenous Immunoglobulin

Treatment of atopic dermatitis with intravenous immunoglobulin (IVIG)

Number of patients	Age	IVIG dose	Outcome	Response time	Duration of remission	Reference
2M,2F	2 - 6 years	0.4 mg/kg for 5 days	all improved	4 - 7 days	1 year	Kimata
3	31 - 40 years	2 g/kg/month	all improved	NA	short lived	Gelfand et al.
1 (child)	8 months	1 g/kg x 1	no improvement	NA	NA	Weiss et al
10	7 - 64 years	2 g /kg x 7	no significant	NA	NA	Wakim et al
19M, 22 F	NA	< 30 kg 0.5 mg/kg >30 kg 15 g x 1	significant improvement	NA	NA	Noh and Lee
5 (children)	7 - 12 months	2 g /kg/month x3	all improved	3 months	> 6 months	Huang et al
3M	19 - 45 years	2 g/kg/month x 11	all improved	2 - 4 months, maximal 11 months	1 year	Jolles et al
6M	18 - 53 years	2 g/kg/month	4/6 improved	2 - 4 months	2/4 > 3 months	Jolles et al
10	18 - 50 years	2 g/kg x 1?	no significant improved	NA	NA	Paul et al

M, male; F, Female; NA, not available

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Typical adverse events

- Headache
- Facial flushing
- Rash
- Fever
- Rigors
- Nausea/vomiting

Reducing the infusion rate can remedy most immediate reactions

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Rare, clinically significant events

- aseptic meningitis
- anaphylaxis- IgA deficient patients
- positive direct antiglobulin test and red cell haemolysis
- acute renal failure- sucrose containing products
- thrombotic events

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IVIG - Safety

- FDA has requested all manufacturers to update their product labeling to include:
  - a revised list of post marketing adverse reactions
  - specific statements under Precautions on:
    - Haemolysis
    - Transfusion - Related Acute Lung Injury
    - Thrombotic Events

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IVIG and Thrombotic Adverse Events

- FDA proposed ‘Precaution’ statement
- CPMP proposed IVIG core SPC warning statement
- Possible mechanisms:
  - Increased viscosity / hyperviscosity
  - Osmolality / sodium content
  - Factor XIa ‘contamination’
- Care should be taken in patients with risk factors for thrombo-embolic disease including hyperviscosity
  - rate of infusion
  - reconstitution resulting in hyperosmolar solution

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Thrombotic Events

"Thrombotic events have been reported in association with IGIV (see Adverse Reactions). Patients at risk may include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, and/or known or suspected hyperviscosity. The potential risks and benefits of IGIV should be weighed against those of alternative therapies for all patients for whom IGIV administration is being considered. Baseline assessment of blood viscosity should be considered in patients at risk for hyperviscosity, including those with cryoglobulins, fasting chylomicronemia/markedly high triacylglycerols (triglycerides), or monoclonal gammopathies [See laboratory tests]."

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Haemolysis

"Immune Globulin Intravenous (Human) (IGIV) products can contain blood group antibodies which may act as hemolysins and induce in vivo coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction and rarely hemolysis. Hemolytic anemia can develop subsequent to IGIV therapy due to enhanced RBC sequestration [See ADVERSE REACTIONS]. IGIV recipients should be monitored for clinical signs and symptoms of hemolysis [See laboratory tests]."

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Transfusion-Related Acute Lung Injury (TRALI)

"There have been reports of noncardiogenic pulmonary edema [Transfusion Related Acute Lung Injury (TRALI)] in patients administered IGIV. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever and typically occurs within 1-6 hrs after transfusion. Patients with TRALI may be managed using oxygen therapy with adequate ventilatory support.

IGIV recipients should be monitored for pulmonary adverse reactions. If TRALI is suspected, appropriate tests should be performed for the presence of anti-neutrophil antibodies in both the product and patient serum [See Precautions:laboratory tests]."

Chromatography

Advantages of Chromatography

- **High level of automation, reliability and reproducibility**
- **Higher purity, higher yields**
- **Additional viral clearance**
- **Endotoxin clearance**
- **Closed systems**

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IVIG - Product Comparison Cohn versus Chromatography

	Cohn	Chromatography
Protein Purity	≥98% IgG	≥99.5% IgG
Aggregates	≤0.4%	≤0.1%
IgA	0.06-0.52 mg/mL	<0.02 mg/mL
IgM	<0.02-0.11 mg/mL	<0.02 mg/mL

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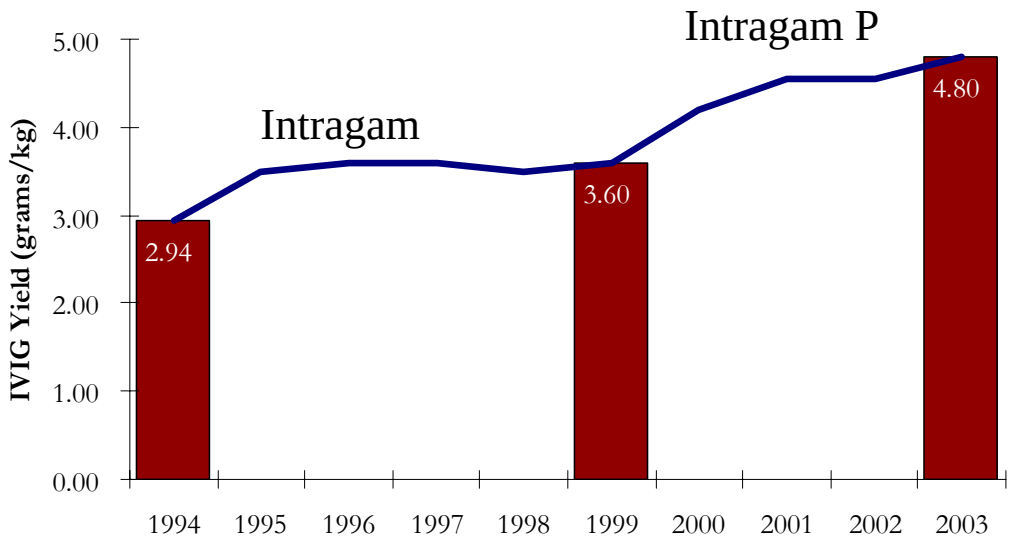
CSL IVIG Yields



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Asia Pacific IVIG Advisory Board

- **The Asia Pacific IVIG advisory Board is an *autonomous* body that will represent the need of physicians in our region in their use of IVIG**
- **At this stage representation includes:**

Australia
China
Hong Kong
India
Malaysia
New Zealand
Singapore
Taipei
Thailand

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Advisory Board Objectives

The key objectives for the advisory board include:

- Developing new guidelines for the use of IVIG
- Creating an IVIG Asia Pacific Conference
- Creating an educational program for the Asia Pacific region
- Providing expert advice to CSL Bioplasma

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