



## Immune Deficiencies Foundation Australia

### PPTA

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Plasma Protein Forum, Washington DC, June 12-13 2018

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#### **JAN BULT**, President, CEO

Need to improve knowledge about:

- Uniqueness of our sector
- Unite people living with RDs that are treated with Plasma Protein Therapies

Need to raise awareness using:

- Policy makers
- Media

“How is your day?” Campaign

#### **DAVID BELL**, Chair, EVP & General Counsel Grifols

- Use Campaign to make a difference
- PPTA represents manufacturers and donation centres
- Mission
  - – is to promote the availability of and access to safe and effective plasma protein therapeutics for all patients in the world. We will strive to achieve our mission by:
    - Fostering the collection of high-quality plasma from healthy donors;
    - Establishing standards for the manufacturing of life-saving plasma protein therapies at the highest levels of safety and quality;
    - Breaking down artificial barriers on trade and compensated donors that limit patient access to therapy;
    - Supporting government reimbursement practices that reflect the unique nature of plasma protein therapies;
    - Educating all stakeholders about the value of the therapies; and
    - Adhering to the PPTA Code of Ethics.
- Establish standards for PPTs
- Break down barriers limiting access to PP
- Education
- 25 years in 2017
- No reported vile transmissions for nearly 30 years
- Maintain commitment to advocacy





**PPTA Lifetime achievement Award** – to JAN BULT - “Nobody can do anything alone – people work with me, not for me”

### **Perspectives – Access to care**

**Tony Castalda**, US HAE Association

HAE

- Rare debilitating potentially genetic disease caused by deficiency in the plasma protein C1 inhibitor
- Mortality rate in undiagnosed/untreated patients – 30%
- Incidence is 1:30,000 – 1:50,000
- Type 1 and Type 11 – clinically undistinguishable – issue in the mutation of C1 gene
- New -Type 111 - HAE with normal C1 inh
- Paediatric disease
- First attack is before age 13
- Swelling:
  - Not mediated by antihistamines
  - Mediated by bradykinin (caused by C1inh)
- First treatment available 2009 USA
- “you feel like you are more of an obligation than a benefit” (patient statement)
- Disease burden survey USA
  - HAE prevented advancement at school or work
  - 20-100 days of incapacitation annually
  - Unpredictability of attacks causes psychological issues – anxiety depression
  - Depression – psychotropic medications common
- CINRYZE (Shire) reduces attacks by 55%
- On demand treatment now available at home
- 2017
- HAEGARDA SC1g (CSL) available (subcutaneous C1INH) 2 x week
  - Trough levels maintained (need to be above 40%)
  - Reduces attacks by 95%

**Joanna Chorostowska-Wynimko** – Professor, Scientific Director National institute of Tuberculosis and Lung Disease Warsaw Poland

Alpha 1 Antitrypsin deficiency

- 3<sup>rd</sup> most rare disease
  1. Down syndrome
  2. Cystic fibrosis
  3. Alpha 1 Antitrypsin deficiency
- Est 3,400,000 worldwide
- PI\*Z Gene
- Scandinavia and Baltic States most prevalent (transferred by Vikings)





- Produced by liver
- Protects lungs
- LUNGS most affected
  - Chronic respiratory disorder
  - COPD
  - Early onset emphysema
- LIVER
  - Chronic hepatitis
  - Cirrhosis
- SKIN
- VASCULITIS
  - – Wegeners granulomatous
- Therapy
- Augmentation replacement therapy 60mg/kg
  - Reduces the protease-antiprotease imbalance
  - Maintain AAT serum
  - Limit/slows down decline of lung function

**Prof Paolo Caraceni** – Assoc Prof Dept Medical and Surgical Sciences, University of Bologna  
Italy

Long term albumin administration improves survival in patients with decompensated cirrhosis

- Liver cirrhosis is the result of chronic liver disease
- Asymptomatic
- Can last for years
- Symptomatic phase
  - Acute liver failure
  - Jaundice
  - Bleeding
  - Bacterial infection
  - Portal hypertension
  - Cardiovascular dysfunction
- Compensated cirrhosis - median survival 12 years
- Mortality
- 1,000,000 deaths per year
- 2/3 under 65 yrs old
- Cost of healthcare in USA over 9mil
- Use of albumin in cirrhosis
  - Acute indication – 1 shot
  - Short term in hospital with albumin
  - Long term use of albumin outside hospital is rare
  - Treatment
  - Modify course of decompensated cirrhosis
  - Reduce organ failure





- Causes:
  - HBC
  - HCV
  - Alcohol
  - NASH
- Albumin molecule
  - Modulation of immune / inflammatory responses
- Trial/study - use of human albumin for patients with cirrhosis
  - 40g 2 x week for 2 weeks then 40g 1 x week
  - IV infusion (30 minutes)
  - Mainly outpatient clinics
  - Significant increase in serum albumin
- 18 months survival rate higher (77%) than others (68%)
- Management of ASCITES (fluid in belly)
  - Drainage of fluid (usual)
  - 62% had no ASCITES in trial – 32%
- Other disease complications reduced
- incidence of complications by 30-67% except for bleeding
- number of days in hospital significantly lower
- QOL improved in study patients
- 3 patients had adverse reactions, but generally well tolerated

### **Current Industry Regulatory Initiatives in the areas of inspections and donor health**

**Ginette Y Michaud**, Director Office of Biological Products Operations, US Food and Drug Administration (FDA)

#### **Form follows function**

- Conduct inspections of plasma collection centres and testing labs
- Follow a compliance program
- Use risk-based approach
- Some facilities have not been inspected for over 2 years
- A form 43 notifies management of objectionable conditions at conclusion of inspection

**Toby Simon**, Senior Medical Director, Plasma & Plasma safety CSL

Donor Health perspectives: Insights from industry plasma vigilance data and future safety initiatives

- USA provides the majority of plasma in the world
- Questions about donor health
- Acute impacts:
  - Immediate or short term impacts from a single donation that result in threats to donor health
- Chronic:





- Are there impacts over time that are a threat to donor health?
- ACUTE IMPACTS
- Haemodynamic changes
  - Vasodepressor reaction
  - Fluid shifts
- Anticoagulant effects
  - Minimal with plasmapheresis
- Cardiac impact
  - Pre-existing cardiac disease exacerbated
  - Hemoconcentration
- Vascular impact
  - Thrombosis
  - Infection
  - Nerve irritation/damage
  - Arterial damage
- 2015 - Developed **donor adverse event reporting standard** to reduce impacts
  - In future use it to develop corrective action
- **Developed Saline standard** – infusion of saline post procedure
  - Hope to reduce possibility of reactions
  - Introduce blood volume
  - Assist iron depletion
- Careful review of fatalities after donation

#### PPTA donor events recording standard

- Detailed categories applicable to plasma industry
- Each plasma organisation as procedures in place to safeguard and monitor the health and safety of donors
- Strengthens the power of data representing plasma industry
- Classifications
  - Hypotensive events
    - Prefaint to loss of consciousness (LOC)
  - Major cardiovascular events
  - Local injury related to phlebotomy event
  - Citrate reaction events
  - Haemolysis
  - Air embolus
  - Allergy event
  - Hyperventilation event
  - Other
- 7.6 mil donations in first analyses
- Adverse events - 20.93 per 10,000 donations
- Hypotensive prefaint 57.3%
- Local injury related to phleb 18.2%
- Hypotensive (LOC) 9%





- Females more likely to experience an adverse event than males
- First time donors more than regular

#### Chronic impacts

- Iron deficiency in whole blood donors
- In plasma donors – protein depletion, esp Igs
- Q: *has the donors immune surveillance been impaired increasing susceptibility to infection and perhaps other problems?*
- Esp in those 2 x week donors
- 25-50% reduction in clotting factors (80-100% recovery at 48 hrs)
- 63% reduct in fibrinogen (65% recovery at 48 hrs)
- 63% reduction in Igs (45% recovery in 48 hours)
- Over time frequent donors experience depletion of Igs
- Drop outs due to time constraints, work, no longer need remuneration
- Total protein not duly affected

#### Donor health study being investigated

**George B Schreiber**, Director Epidemiology, PPTA

Iron depletion in Source plasma donors; A non sequitur.

- Study was done on ferritin levels due to concerns that long term donors could become iron deficient
- Female frequent donors have higher ferritin levels than donors with no donations
- Male frequent donors had lower ferritins than those with lower donations, however the differences were not statistically or clinically significant
- Whole blood donors – after 2-3 donations, iron levels dropped

#### Ferritin levels in plasma donors study (FLIPD)

- High frequency donors – high 1
- High frequency donors – high 2 (greater than 70 donations pa)
- Age increase from no donation to high 2
- Ferritin levels lower in women, but get higher for younger women who donate more frequently
- ? iron supplementation for donors

I asked the question “*were the people in the study asked if they were currently taking an iron supplement?*” *The answer was no.* So I am not sure I find the data a relevant.





## International Access to care landscape

**Professor Martin Van Hagen** Head, Clinical Immunology Dept of Internal Medicine, Erasmus Medical Centre Rotterdam, The Netherlands

### New Criteria CVID

- **Autoimmunity new criteria for CVID**
- PIK3CD, gain of function mutation – boy autoimmune, lupus, bowel disease, liver new treatment -Leniolislab
- STAT 3 mutations
- Hyper IgE
- Polyp in gut – related to STAT 3 as is tumours
- PID – ENDI genes (hormone disorders) similar genes
- Ig replacement
- Immunosuppressives
- FcRn function – used to transport IgG
- granulocytes involved in metabolism of IgG

**Dr Ranjeet S Ajmani** EO PlasmaGen Biosciences Pvt Ltd

Initiatives to improve access to care in India

- 1.3 billion people
- 22 languages
- 29 states and territories
- 70% live in rural areas
- Collects 11 mil units of blood per yr
- Blood must stay with its particular blood bank
- A lot of blood is wasted
- Human blood is considered a drug under India law
- 2900 blood collection centres
- Wastage 3%
- repeat donor base 25-30%
- Plasma 1.74mil lt
- 35% clinical use of plasma
- 60% whole blood usage
- 350% growth in Ig use 2015-16
- 22.8 mil births in 2017
- Current blood shortage





**Antonio Condino-Neto** President Latin American Society for Immunodeficiencies (LASID)  
**What needs to be done to improve access to immunoglobulin therapy in Brazil?**  
**Diagnosis, access and supply**

Brazil

- Population 208,617,200
- 5570 municipalities
- Infant mortality 14.6/1000
- Life expectancy 74 years
- 7633 PID cases since 2009
- Active education program for physicians
- 128 JMF centres
- 65% pred antibody deficiencies
- 9% combined immunodeficiencies
- 10% well defined syndromes
- Health is covered by the State
- 100% imported plasma
- There are plasma fractionation companies in Brazil (CSL, Oct, Grifols, Kedrion, Biotest, BPL, Hemobras)
- Stringent Brazilian Laws against fractionation
- Import plasma from USA and Korea
- Issues – Zika virus – Ig has no antibodies to this
- Need to change the Brazilian Constitution
- Ig purchase up 200% 2008-2014

NOTE:

- *Australia no 2 in the world for Ig consumption*
- *1927 patients followed by JMF in Australia*

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**Dr Otto Swartz winner:** Shinji Wada (Grifols) for his contribution to the plasma industry

Repugnant transactions and forbidden markets: different tissues, same issues **Alvin E Roth**  
**Nobel Prize winner – economic sciences**

- Markets need social support to function well
- Some Canadian States banning payments for plasma and blood donation
- WHY? Concerns:
  - Exploitation
  - Commodification
  - Objectification
  - Contamination
  - Creating a “slippery slope”







- Repugnant transactions – if some people want to engage in a transaction and others don't think they should be allowed to (even if the transaction doesn't cause any easily measured harm).
  - Other examples include:
    - Same sex marriage
    - Surrogacy
    - Donating an organ
    - Claiming cadavers for medical science
    - Lending money for interest (was once illegal)
- **Often x+\$ is repugnant even when x alone isn't.**
  - E.g. interest on loans
  - Prostitution
  - Surrogacy
    - In Canada it is legal but you can't be paid for it
    - You must be over 21
    - In California you can buy sperm, eggs, and a surrogate and have your name on the birth certificate
  - Donating plasma
  - Donating a kidney
    - US shortage – 100,000 people on the waiting list for a kidney
    - Only 12,000 transplants per year
    - 6,000 additional transplants from living donors
    - Sometimes donors are incompatible with the recipient
    - Kidney exchange program
    - Worldwide 2.7 million people die every year due to inability to pay dialysis or kidney transplantation
    - Kidney exchange achieves the benefits without using money and thus without running into the barrier caused by the repugnance that kidney sales arise
    - Kidney exchange can cross borders
    - However cross border exchange is defined as organ trafficking
  - Donating bone marrow/stem cells
    - Some donors of stem cells can be paid
- In Germany only family members can donate
- In Europe .. the human body and its parts shall not as such give rise to financial gain
- Repugnancy is a potential threat to access and availability of Plasma Protein therapies
- When repugnancy is an issue, transactions can have their status change from acceptable to repugnant
- E.g. surrogacy for foreigners in Asia
- When discussing payment for plasma, talk about the donors, their dignity, motivation
- We need to maintain a diverse pool of donors





## Current Challenges

**Prof Dr Liu Zhong** VP Institute of blood transfusion Chinese Academy of Medical Sciences (CAMS)

Which is safer source plasma for manufacturing in China: Apherisis plasma (plasma fractionation - PAID) or recovered plasma (separated from whole blood – NON PAID)

- Research project before policy making
- All plasma for fractionation is collected by plasma centres
- 7mil l of AP collect4ed
- 10mil l needed annually
- Can the plasma from RP be used? 4 problems
  - Technique
  - Law
  - Ethics
  - Administration

To evaluate SAFETY

Design of study

Residual risks

- HIV
- HBV
- HCV

Risks

- HAV/B19
- HEV
- WNV/SFTSV
- HCMV

RR – residual risk

**Chen Bin** Deputy Director Medical Safety and transfusion Division Dept of Medical regulatory and Management, National Health Commission

The current situation and challenge of the Chinese plasma management

- 1960s first plasma product manufacturing plant established
- 1980's banned imported blood to due HIV crisis
- 1990s introduced regulations on the management of blood products, used machines to collect plasma, compliance requirements for blood product companies
- 2000s plasma technology operating procedures, apheresis plasma centres quality management specification
- GOAL quality safety and adequate supply
- Principle
  - Scientific development





- Overall coordination
- Fair accessibility
- Safety and effectiveness
- MEASURES
  - Establish legal system
  - Improve planning

#### Blood centres

- Set up by government
- Blood tested/screened 3 times – HIV, HepB and other diseases -
- Supplied to clinics for patients
- Non profit

#### Plasma Centre

- Set up by blood product manufacturing company that collects source plasma for manufacturing blood products
- Cannot be supplied to blood centres

Sometimes a plasma surplus,

Aim to be self sufficient (1.3 billion population)

1. Concerned about safeguard of quality and safety of blood
2. Immunisation factorisation
3. Meet social ethics requirements

#### Two systems

- Laws
  - Criminal law
  - Blood donation law
  - Issued by Central govt
- Regulations
  - On blood management
  - Methods
  - Quality management
  - Operating procedures

#### Blood centres

- 452 blood centres
- 1380 fixed collection sites
- 1593 collection vehicles (to Universities)

#### Apheresis

- 260 centres





- Covering 650 cities
- And 360 million people in those cities

#### Voluntary non remunerated blood donations

- 14.59 mil in 2017
- Pre-donation consultation and screening, blood condemnation rate is 5.3%
- Clinical transfusion rate of blood components 99.8%

#### Source plasma collection

- Increasing to 8,000 tons in 2017
- Av annual growth rate 13%

#### 5 gateways to safety of blood products

1. Selection of donors
2. Testing
3. Quarantine period
4. Virus removal
5. Reasonable use

#### Outlook for the future

1. Share effective policies of blood safety and sufficiency
2. Promote national blood system construction from different levels
3. Strengthen cooperation and exchange of blood safety products
4. Establish an effective communication platform promote blood safety information exchange
5. Establish standardized procedures and processes

#### One goal

- Safe and adequate supply of plasma

#### Two frameworks

- Legal framework
- 'setting up plans
- Low risk donors

#### Three pillars

- SCREENING STRATEGIES
- REASONABLE USE
- BALANCE BETWEEN COLLECTION AND SUPPLY
- Comprehensive utilisation





## **Peter Jaworski Prof, Georgetown University, Washington DC**

### **Ethics of compensation for blood donation**

- Paid plasma is ethical
- Protecting access to immune globulins for Canadians publication
- Paid plasma is safe
- No good evidence that paid plasma negatively affects unpaid collection
- It is unlikely that unpaid plasma donation will result in self sufficiency

## **Joshua Penrod, VP, Source and International Affairs, PPTA**

### **Global sufficiency**

- Patients are forgotten
- Donors – are people
- Plasma centres – dens of iniquity??
- 660 plasma centres in the US
- In Europe 107 plasma collection centres
- 290.3 metric tons needed for 2024
- Marketing research bureau data
- Much growth in plasma centres and need
- Titmuss wrote.. – voluntary non-compensated donation the only moral way to collect blood
- Fails to realise that humans have multiple reasons for what they do and their decisions can change
- Canadians
  - Exclusion in Quebec, Ontario, Alberta, British Columbia

A handwritten signature in blue ink that reads "C. Jeffery".

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