

LESS IS THE NEW MORE FOR IVIg !!

TIME FOR LEAN BODY WEIGHT DOSING ?

Dr D Lynn Aston
THE BLOOD SERVICE WA NT

WHY ARE WE HERE

?

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HERE ?

TRANSFUSION UPDATE 2010

- ALL INTERESTED IN TREATING PATIENTS

WITH “BLOOD” or ALTERNATIVES

- APPROPRIATE PRODUCT

- APPROPRIATE DOSE

OBLIGATIONS TO OUR PATIENTS

- SAFETY
- Efficacy
- Adequacy of supply
- Equity of access. Between and within states
Public or Private patients
- All products free of charge at point of use



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BLOOD
BANK

SORRY, I CAN'T GIVE YOU
A TRANSFUSION ~
YOUR ACCOUNT IS ALREADY
OVERDRAWN.

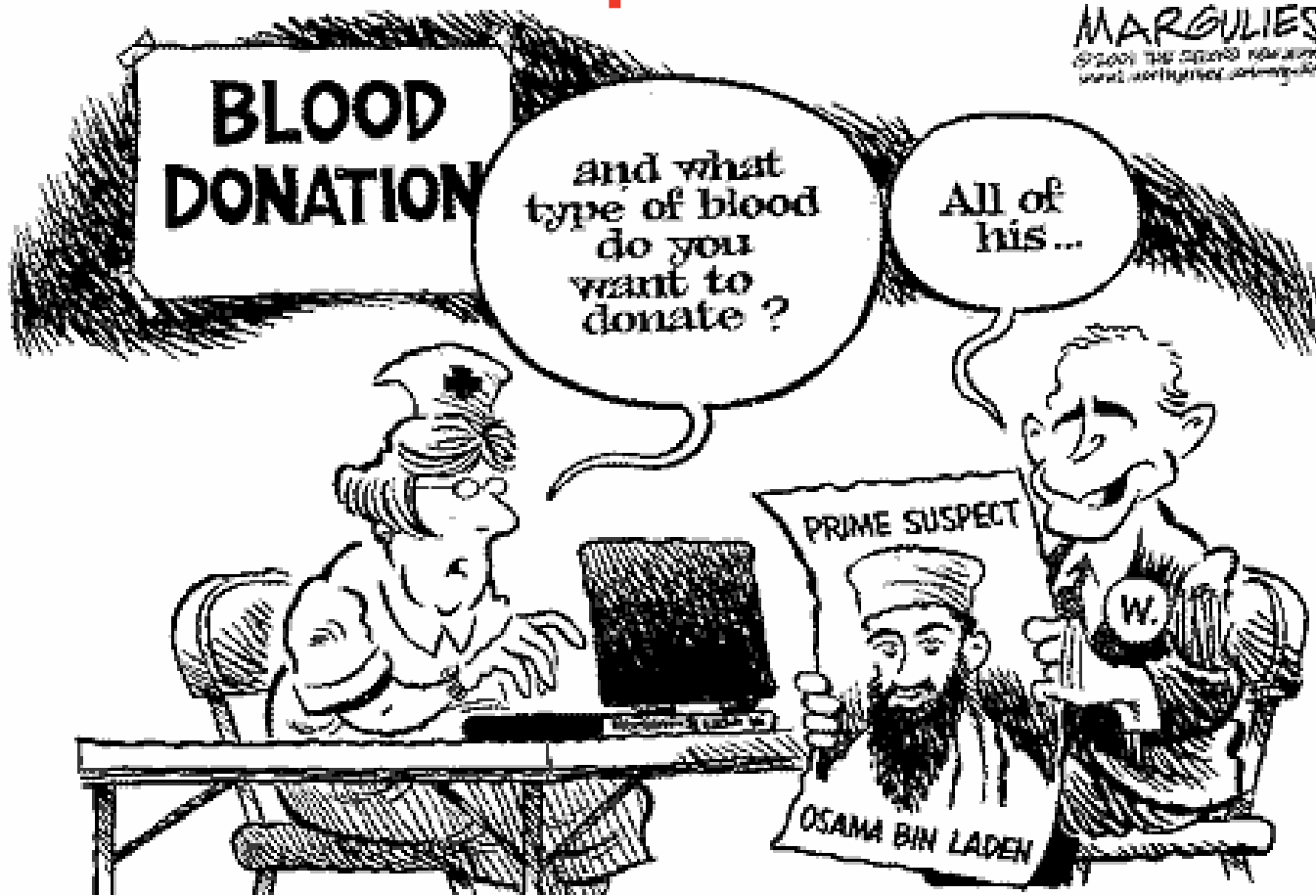


OBLIGATIONS TO OUR DONORS

- Stewardship of Life's greatest gift
- Maximise usage
- Minimise wastage
- Care and safety of our voluntary, non remunerated donors

Donors are Selected as Whole Blood or Apheresis

AHAJOKES.COM



PLASMA FOR FRACTIONATION

- The driver is **IVIg**
- The Blood Service collects

over 400 tonnes !!!

OBLIGATIONS TO OUR FUNDERS

Ultimately the taxpayers !!

- Cost effective products
- Overall cost control
- Minimise Wastage
- Innovation

FACTORS TO CONSIDER

- National Self sufficiency in Blood and Blood Products
- Difficulties with world supplies in past
- Cost of this product over \$ 150 Million
- Voluntary non remunerated donors
- 1.5 Gm IVIg per whole blood donation
- 3.0 Gm IVIg per plasmapheresis collection

THE NATIONAL BLOOD AGREEMENT

- PROVIDES
Adequate, safe, secure and affordable “blood”
- PROMOTES
Safe, high quality management and use of “blood”



Australian Health
Ministers' Conference

Criteria for the clinical use of **intravenous immunoglobulin** in Australia

www.nba.gov.au

December 2007

 Australian Red Cross
BLOOD SERVICE

CRITERIA FOR CLINICAL USE OF IVIg

- Prescriptive
- Evidence based
- Minimum effective dose and duration
- Currently under review

THE CRITERIA - OUR BIBLE

- Conditions approved for IVIg supply
- Detailed qualifying and exclusion indications
- Doses for induction and maintenance
- Duration of therapy and review

LEAN BODY WEIGHT DOSE ADJUSTMENT

- Lean body weight
actual weight less ALL adipose tissue
- Ideal body weight
initially P P Broca 1871 desirable, healthy
then B J Devine 1974 for medication





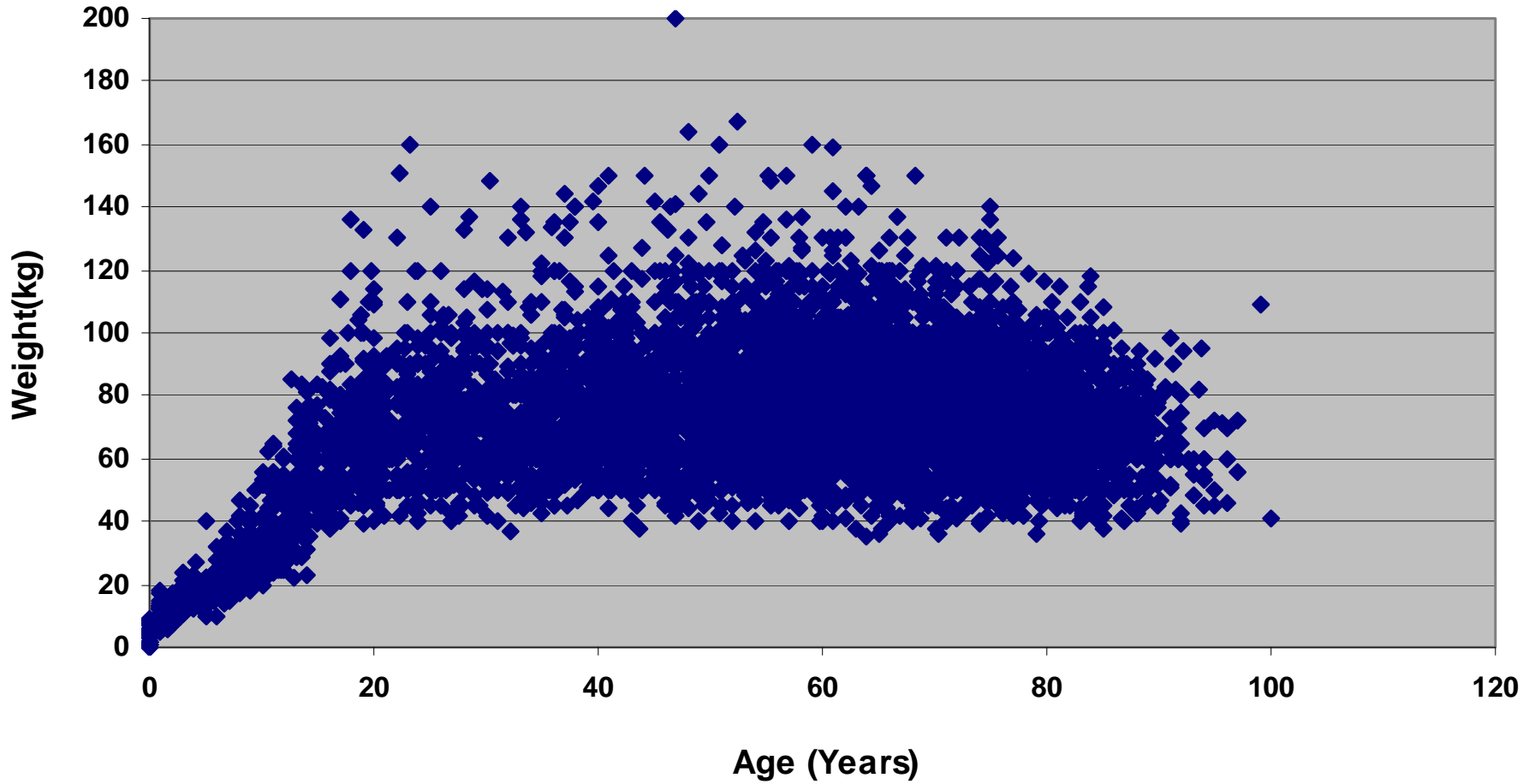




i'm lovin' it



IVIG Recipients - Age vs Weight



IVIg PHARMACOKINETICS

- Clinical response to “arbitrary” dose
- Peak plasma levels
- Area under the curve
- Persisting levels
- Half-life
- Catabolic rate

IVIg PHARMACOKINETICS

- IVIg distributed in Vascular and extra-cellular spaces
- Very poorly distributed in adipose tissue
- High dose IVIg (2 Gm/Kg) can cause hyperviscosity
- Increasing obesity, particularly in the elderly who are also increasing !
- IVIg use skewed to elderly

LEAN BODY WEIGHT DOSE ADJUSTMENT

- UCLH Institute of Neurology Queen Square
- International shortage of IVIg in 2005-6
- Introduced a formula for Gentamicin dosing using Devine's modification to Ideal Body weight
- No lack of effect for initial 2 G/Kg doses
- Subsequently retained
- **Draft** UK IVIG Guidelines had formula in 2007
- Omitted due to lack of evidence base

The effect of the introduction of the *Criteria for the Clinical Use of Intravenous Immunoglobulin (IVIg) in Australia* on the supply of IVIg in Western Australia

D Lynn Aston, Julianne Lefante and Annie McNaë

On behalf of ARCBS Transfusion Medicine Services in Western Australia (WA TMS), Australian Red Cross Blood Service (ARCBS), Perth.

Background

Intravenous immunoglobulin (IVIg) in Australia is produced from the plasma of volunteer donors and is an invaluable resource. In 2005 Australia was the fourth highest user per capita in the world and with recent annual national increases as high as 15 percent, meeting demand with domestic product has been challenging, requiring supplementation with imported product.

In December 2007, the *Criteria for the clinical use of intravenous immunoglobulin in Australia* was developed with contributions from interested parties including ARCBS under the auspices of the Jurisdictional Blood Committee (JBC). The *Criteria* document which was approved by the Australian Health Ministers' Conference was implemented nationally in March 2008.

This evidence-based document identifies those conditions and circumstances for which IVIg can be accessed under the National Blood Agreement. IVIg is funded by the National Blood Authority on behalf of the governments of Australia and is provided at no direct cost to patients with a qualifying diagnosis as listed in the *Criteria*. A list of diagnoses for which there is no proven benefit are available in Chapter 8. These are not funded under the National Blood Agreement. The ARCBS Transfusion Medicine Services teams have played an integral role in implementation of and compliance with the *Criteria* across Australia, relating to clinical authorisation of IVIg use and follow-up.

A period of treatment for clinical and, if appropriate, immunological reassessment, may be mandated under the *Criteria*. This cessation of treatment after a period during which the patient has appeared to benefit while receiving IVIg has been a source of some anxiety for both patients and treating clinicians, and for some indications the "clarifications" of the *Criteria* have allowed the IVIg to continue until the next summer period to reduce the risk of possible infections.

Implementation

The *Criteria* were implemented in March 2008 allowing a six month transition period for the review and assessment of current patients' eligibility to receive National Blood Agreement funded IVIg.

In WA stocks of IVIg are held at ARCBS and each individual patient request is approved before release of the product. The doses for long term patients are supplied on demand within a week before the due date. A file is kept for all patients who have had a request for IVIg whether approved for long-term or one-off treatment or referred for a Jurisdictional Direct Order. The file contains the request form, referral letters, laboratory results and reviews and any other correspondence and relevant information. All information about IVIg issues are captured in the ARCBS national STARS (Supply Tracking Analysis and Reporting) database.

Methods

A detailed review was undertaken for all existing WA patients using the WA TMS records of diagnostic information and the STARS database to ensure they conformed to the new *Criteria*.

Extensive communications between ARCBS TMS staff and treating clinicians were necessary. Some 500 letters were written to request specific information which had not been required when the patient initially commenced IVIg or to request reviews in addition to the regular proforma requesting follow-up details. Email proved a rapid and usually successful means of communication and telephone calls to consultant clinicians' mobiles were often used in cases of urgency or complexity.

The scope of the operation was larger than originally estimated by all parties with the six month transition period identified as difficult to attain and additional nursing hours were required to assist with this review task. Dissemination of the existence of the *Criteria* was challenging, and in large public hospitals the rapidly rotating junior staff were often unaware of the *Criteria*. Managing concerns of clinicians and patients ahead of required changes, particularly withdrawal from treatment on a trial or permanent basis was sometimes difficult and time-consuming. Certain ambiguities and anomalies requiring "clarification" further lengthened the "reclassification" period at times.

Results

At the start of the period 363 patients were actively receiving IVIg, some regularly, some sporadically and some long-term. 150 of these were found to be nonconforming to the new *Criteria* and 92 ceased treatment as they no longer qualified. 54 of these patients had diagnoses of IgG subclass deficiencies, all with a history of prolonged severe chest complications, usually under control while on IVIg. These patients and their physicians were understandably very anxious about ceasing therapy even in the next summer period as allowed in the clarifications. None of these patients who were stopped has needed to restart IVIg, which has been reassuring to patients and their physicians. In a very few patients where it was felt the risk was too great to consider cessation for re-evaluation they continued in a new classification of "existing IgG subclass patients". During the 15 month period from March 2008 to June 2009, 265 new patients commenced IVIg for a range of indications, and at the end 343 patients were on treatment, 280 of them long-term.

IVIg has always been an "intensively managed" product by ARCBS, but even more so over the last two years. A total of 2132 kg of IVIg were supplied nationally in 2007/08 and 2364 kg in 2008/09 an increase of 11 percent. In WA, 187 kg were supplied in each year an increase of zero (0) percent.

In addition to differences in rates of increase between the jurisdictions there is also considerable variation in the rate of supply in grams per 1000 population. There are many reasons for these variations and these are currently being considered.

The rates of supply in g/1000 population are presented for the last six years for WA and nationally with variations from the preceding year. (See Figure 1 and Table 1.)

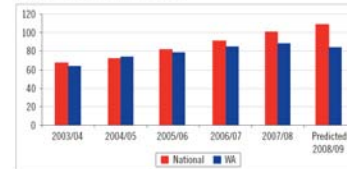


Figure 1: IVIg supplied (grams per 1000 population)

Table 1: Percentage variation on previous year

	2004/05	2005/06	2006/07	2007/08	2008/09
National	7%	11%	11%	9%	8%
WA	14%	6%	8%	3%	-4%

Lean body weight adjusted dosing

A pilot project was initiated in WA with the consent of treating clinicians in each case to reduce the dose in obese patients. While there is no published evidence on this approach with regard to IVIg, chemotherapy and other drugs with a narrow therapeutic index are usually dose-adjusted by surface area or another formula to allow for the poorly perfused excess adipose tissue. The Institute of Neurology in London has used a formula based on gentamicin dosing in the obese for three years and not detected any reduction in efficacy in neurological conditions (personal communication). Obesity is a growing problem in Australia and worldwide and it seems sensible to dose agents such as pharmaceuticals and biologicals at the lowest effective dose. This is one of the principles of the *Criteria* and this approach should also contribute to minimisation of side-effects, some of which may be dose-related.

Conclusion

The introduction of the *Criteria* has been a time-consuming task. In WA the ARCBS medical specialist, nurses and administrative assistant have all played important roles in propagating the *Criteria* (including ordering copies for physicians – available for order from the National Blood Authority website www.nba.gov.au), discussing the implications with clinicians and in some cases with patients, and ensuring regular reviews and dose adjustments are being carried out.

The application of the *Criteria* with some contribution from lean body weight dose adjustment has halted the expected increase in use of IVIg in WA saving the plasma from some 13,000 donors and also substantial costs.

The ARCBS TMS team in WA continues to work closely with local clinicians to ensure eligible patients receive adequate but lowest effective doses of IVIg and to minimise the seemingly inexorable increase in use of this scarce and invaluable resource.

References: Australian Health Ministers' Conference 'Criteria for the clinical use of intravenous immunoglobulin in Australia', December 2007; Australian Red Cross Blood Service Annual Report 2007-2008; and National Blood Authority Australia Annual Report 2007-2008

Acknowledgement: The exceptional support in data entry and record keeping from our Administrative Assistant Kathryn Hamilton in preparation of this work is gratefully acknowledged.

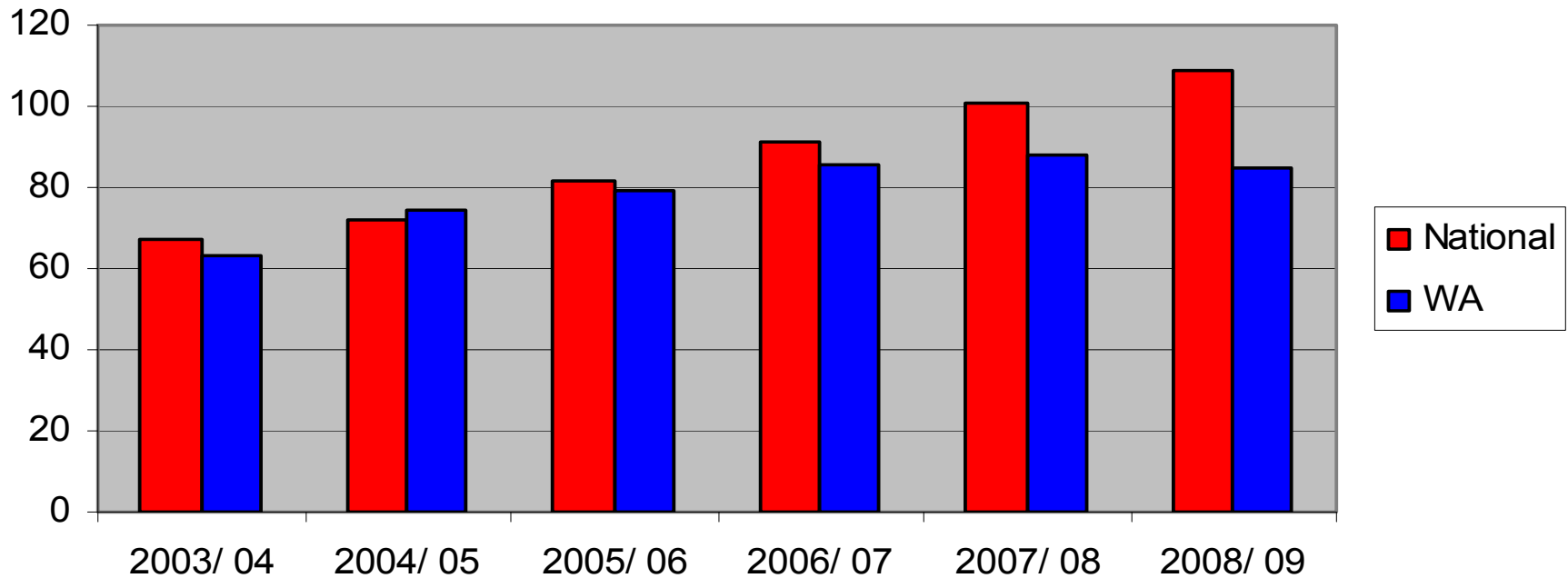
For more information visit
transfusion.com.au

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IVIg SUPPLIED IN AUSTRALIA

IVIg Supplied (grams per 1000 population)



PILOT STUDY IN WESTERN AUSTRALIA

- All new patients who are “**short for weight**” and **where applicable** existing patients converted
- Individual patients discussed with specialist. All agreed
- No lack of effect noted in initial dose
- Doses are titrated to “lowest effective” for maintenance

**INTRAVENOUS IMMUNOGLOBULIN (IVIg) REQUEST FOR
IMMUNOLOGICAL OR GENERAL INDICATIONS**

IMMUNOLOGICAL OR GENERAL INDICATIONS

PLEASE FAX COMPLETED FORM TO (08) 9421 2847 or (08) 9221 1215

Please follow up Urgent Orders by phone

ARCBS CONTACT (8.30am - 4.30pm): (08) 9421 2377 After Hours Phone: (08) 9325 3030 or (08) 9325 3333

MUST BE COMPLETED

PATIENT Weight = _____ kg Height = _____ cm

DELIVERY INSTRUCTIONS

HOSPITAL / LABORATORY RECEIVING IVIg

PH (0)

FAX (0)

PATIENT DETAILS OR AFFIX HOSPITAL LABEL

SURNAME

FORENAME

SEX M F

UR _____ DOB / /

HOSPITAL

Previous IVIg Yes No Please indicate date / / and response

Immunologist confirming diagnosis

Treating Specialist

Requesting Medical Officer Name

Signature

Phone (0)

Pager/Mobile

Fax (0)

Date / /

DOSE DETERMINING WEIGHT

- Calculate Ideal Body Weight (I B W)
- Add 40% difference between actual and I B W
= Dose Determining Weight D D W
- Excel calculator
- Equates to $36 \text{ G} / \text{m}^2$ by BSA nomogram

CALCULATION FOR IBW AND DDW

ADD WGT IN KG AND HGT IN CM

Female IBW

Height in cm	155.0
Height in inches	61.0
Weight in kg	98.0
IBW	47.9
Dose Adj Wgt	67.9

Male IBW

Height in cm	180.0
Height in inches	70.9
Weight in kg	98.0
IBW	75.0
Dose Adj Wgt	84.2

0.4 g/kg	27.2
0.5 g/kg	34.0
1 g/kg	67.9
1.5 g/kg	101.9
2 g/kg	135.8

0.4 g/kg	33.7
0.5 g/kg	42.1
1 g/kg	84.2
1.5 g/kg	126.3
2 g/kg	168.4

REDUCTION IN USE OF IVIg

- 20 Kg less than plan in 2008-9
- 40 Kg less than plan in 2009-10 ?
- 10 Kg absolute less in 2009-10 ?
- Ideal body wt dosing “saving” 4 Kg
= 2700 plasma donations

TIME FOR LEAN BODY WEIGHT DOSING

?

TIME FOR IDEAL
BODY WEIGHT
ADJUSTED DOSING
!

CURRENT SITUATION

- No evidence base - yet
- Studies needed
- Worth considering in all obese patients
- Interest in UK and Canada

WHY ?

- Individualising APPROPRIATE dose for each patient
- Reduces unnecessary WASTE
- Reduces unnecessary COST
- Aids SELF SUFFICIENCY in blood and products
- Helps availability for inevitable new indications

ACKNOWLEDGEMENTS

- Australian Red Cross Blood Service colleagues
 - T M S W A and N T team
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 - Dr Marija Borosak (Victoria) lead for TMS IVIG Working Group
 - David Jones (South Australia) manager STARS database
- and
- Ms Evelyn Frank Institute of Neurology, UCLH, London
 - Dr Michael Lunn

DUTCH GUILLAIN-BARRE STUDY

Kuitwaard, K et al, Ann Neurol 2009; 66: 597-603

- Post-hoc analysis 174 pts out of 372
- Suggested higher increments in total IGG levels on day 14 correlated with better course and results at 6 months
- Suggest prospective randomised studies
- Looking into effect of ideal body wt.
 - ? Higher increments in obese pts who were “overdosed”.
 - ? May need > 2 Gm/Kg adjusted dose

MODE OF ACTION OF IVIg

- Numerous contenders
- Fc(gamma) receptor blockade
- Sialated Fc IGg upregulates **inhibitory** Fc receptors on effector cells in mice and in humans via dendritic cells receptors DC-SIGN
- Jeffrey Ravetch ?? IVIg X 10
?? recombinant

PERTH FORESHORE

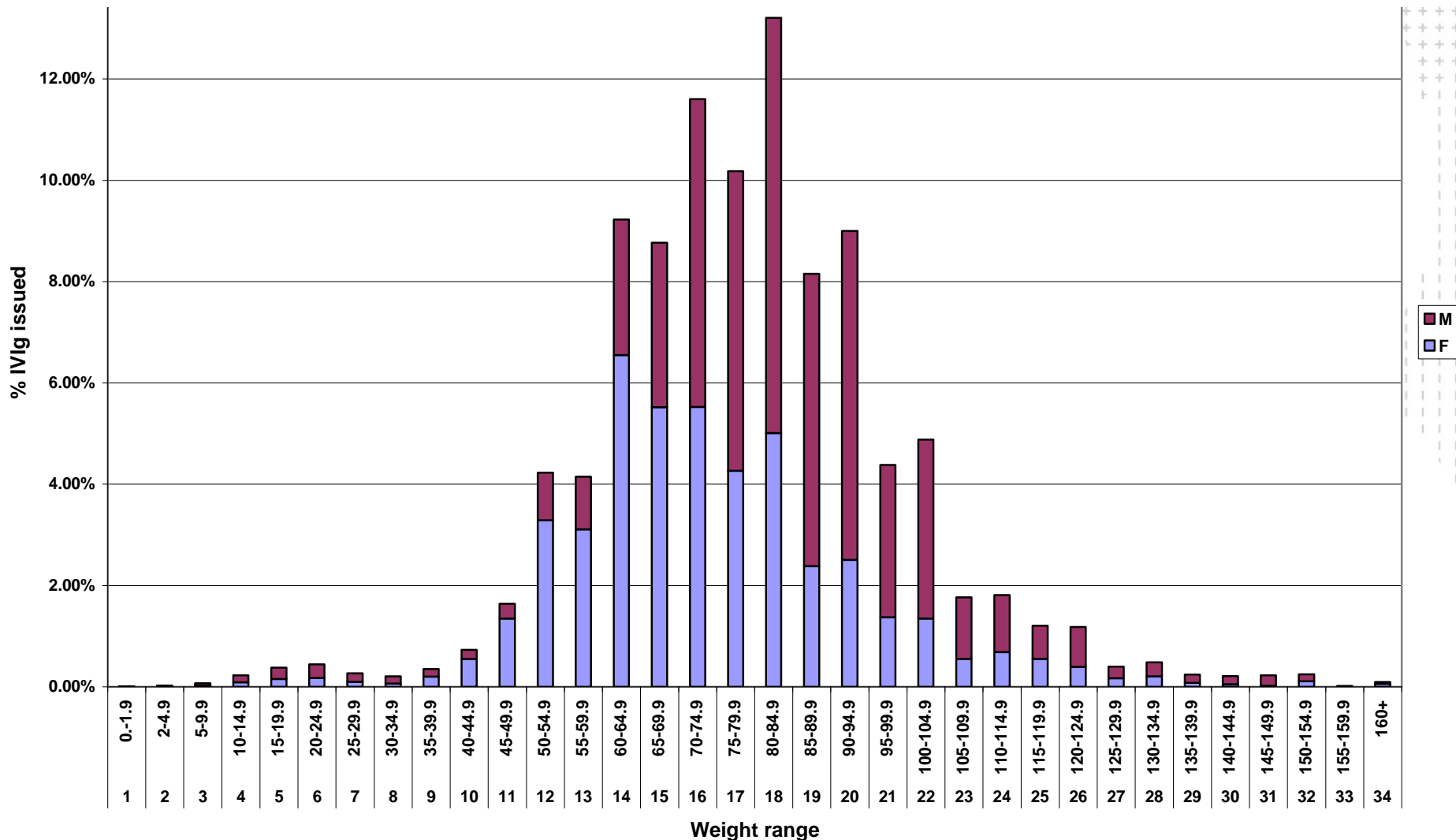
... AND THIS
IS THE TOMB
OF THE
"UNKNOWN
PATIENT..."

CARPS THE BUILDER

Allen

IVIg use by patient weight ranges

- all disease indications (Jan 07 - Jun 09)



37.2% ≥ 80 Kg

26.0% ≥ 90 Kg

12.6% ≥ 100 Kg

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