Appropriate Use of IVIG and Albumin

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Introduction

- Intravenous immunoglobulin G (IVIG) consist of sterile, purified, concentrated, immunoglobulin G obtained from more than 1000 donors that are pooled together.
- It has been used in the management of patients over the last 60years.
- At present IVIG is effectively used and broadening in indications to treat a variety of autoimmune diseases, immune deficiencies, infections and host of other medical conditions.

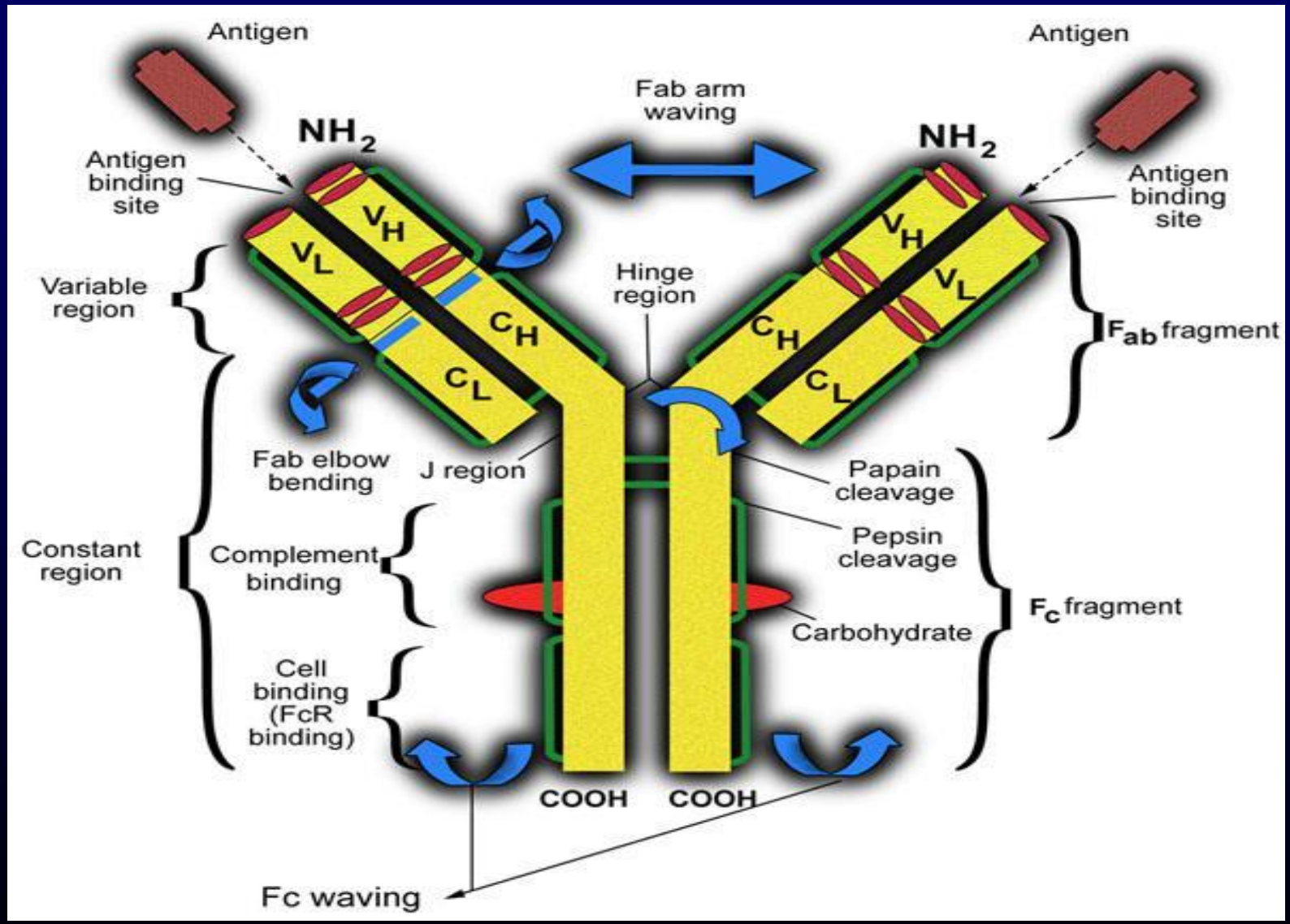
Critical Points

- Immunoglobulins produced by B cells: essential for adaptive immunity.
- In appropriately selected cases, IVIG can be life saving and the 1st choice for treatment
- Antibody replacement and immune modulation
- Even so, there are adverse effects and significant costs in using IVIG.
- Therefore, availability of guidelines for selection of patients in whom IVIG should be used, is very important.

Objectives of Clinical Guidelines

- appropriate use of IVIG and a framework for the promotion of Evidence Based Medical (EBM) practice to help improve consistency in patient care.
- The goal of this GL is to ensure best practice in the use of IVIG across all indications, based on available evidence and expert opinion.
- The overall objective is distinct from other disease-specific guidelines, which seek to provide recommendations on how best to manage a single disease.

Structure of immunoglobulin G



Current Joint UK Blood Transfusion and Tissue Transplantation (JPAC) Guidelines

- High-priority (‘red’) indications for intravenous immunoglobulin – adequate evidence base and potentially life-saving

Primary and secondary antibody deficiency states	**Primary immunodeficiencies** **Thymoma with immunodeficiency** **HSC transplant in primary immunodeficiencies** **Specific antibody deficiency**
Haematology	Alloimmune thrombocytopenia (feto-maternal/neonatal) Haemolytic disease of the newborn Idiopathic thrombocytopenic purpura (ITP) – acute and persistent
Neurology	**Chronic inflammatory demyelinating polyradiculoneuropathy (acute)** **Guillain–Barré syndrome** **Paraprotein-associated demyelinating neuropathy**
Others	Kawasaki disease Toxic epidermal necrolysis

Blue' indications for intravenous immunoglobulin – a reasonable evidence base but other treatment options may be available

Primary and secondary antibody deficiency states	Secondary antibody deficiency (any cause)
Haematology	Acquired red cell aplasia: parvovirus Autoimmune haemolytic anaemia Clotting factor inhibitors Haemophagocytic syndrome Post-transfusion purpura
Neurology	polyradiculoneuropathy (chronic) Inflammatory myelopathies Myasthenia gravis Multifocal motor neuropathy Rasmussen syndrome Stiff person syndrome

‘Blue’ Indications for IVIG

Others	**Autoimmune congenital heart block** **Autoimmune uveitis** **Immunobullous diseases** **Necrotising staphylococcal sepsis** **Severe or recurrent Clostridium difficile colitis** **Staphylococcal or streptococcal toxic shock syndrome** **Antibody-mediated rejection after solid organ transplantation**

Clinical Guidelines for IVIG Use – NHS England

National Demand Management Programe For IVIG Use 2nd Edition 2008

Updated Version 2016

Red
High priority

Conditions	Short term	Long term
Alloimmune Thrombocytopenia (Foeto - Maternal/Neonatal)		
Chronic inflammatory demyelinating polyradiculoneuropathy		
Gullian-Barre Syndrome		
Haemolytic disease for the newborn		
HSCT in primary immunodeficiencies		
Immune thrombocytopenic pupura (acute and persistent, excluding chronic*)		
Kawasaki disease		
Paraprotein - associated demyelinating neuropathy (IgM, IgG or IgA)		
Primary immunodeficiences		
Specific antibody deficiency		
Thymoma with immunodeficiency		
Toxic epidermal necrolysis, stevens Johnson syndrome		

*Updated February 2016

Blue
Medium priority

Conditions	Short term	Long term
Acquired red cell aplasia		
Autoimmune congential heart block		
Autoimmune haemolytic anaemia		
Autoimmune uveitis		
Coagulation factor inhibitors (allonatibodies and autoantibodies)		
Haemophagocytic syndrome		
Immunobullous disease		
Inflammatory myopathies		
Multifocal motor neuropathy		
Myasthenia gravis (including Lambert - Eaton myasthenic syndrome)		
Necrotising (PVL - associated) staphylococcal sepsis		
Post - transfusion purpora		
Rasmussen syndrome		
Secondary antibody deficiency (any cause)		
Severe or recurrent clostridium difficile colitis		
Staphylococcalor Streptococcal toxic shock syndrome		
Stiff person syndrome		
Transplantation (solid organ)		

Grey
Low Priority

Conditions	
Immune-mediated disorders with limited evidence of immunoglobulin efficiency	Presumed immune-mediated disorders with little or no evidence of efficiency
Acute disseminated encephalomyelitis (If high dose steroids have failed)	Acquired red cell aplasia not due to parvovirus B19
Autoimmune encephalitis (including NMDA and VGKC antibodies, among others) Catastrophic antiphospholipid syndrome	Acute idiopathic dysautonomia
Cerebral infection with antiphospholipid antibodies	Aplastic anaemia/pancytopenia
Chronic ITP	Atopic dermatitis/eczema
CNS Vasculitis	Autoimmune neutropenia
Complex regional pain syndrome	Chronic facial pain
Neuromyotonia	Diabetic proximal neuropathy
Intractable childhood epilepsy	Haemolytic uraemic syndrome
Opsoclonus Myoclonus	PANDAS
Post exposure prophylaxis for viral or pathogenic infection if intramuscular infections is contraindicated, or treatment when hyper-immune	Paraneoplastic disorders that are know not to be B- or T-cell mediated
Immunoglobulins are unavailable	POEMS
Pyoderma gangrenosum	SLE without secondary immunocytopenias (Including juvenile)
Systemic juvenile idiopathic arthritis	
Systemic vasculitides and ANCA disorders	
Urticaria (Severe, intractable)	

Black

Conditions
Immunodeficiency secondary to paediatric HIV infection
Autologous BMT
Adrenoleukodystrophy
Alzheimer's disease
Amyotrophic lateral sclerosis
Critical illness neuropathy
Multiple sclerosis
Rheumatoid arthritis
Neonatal sepsis (prevention or treatment)
Sepsis in the intensive care unit not related to specific toxins or C. difficile
Asthma
Graves ophthalmopathy IVF failure
Recurrent spontaneous pregnancy loss

Version .2.

American Guidelines:uses of IVIG

Neurological Conditions	Immunological conditions	Haematology	Others
GBS	Primary immunodeficiencies	Malignancies-Chronic lymphocytic leukaemia, non-Hodgkin lymphoma	Allogenic bone marrow transplant
Chronic inflammatory demyelinating polyneuropathy	Eg. Common variable immunodeficiency (CVID)	Myeloma	Vasculitis
Multifocal motor neuropathy	Secondary/ acquired immunodeficiencies	Immune thrombocytopenia	Kawasaki disease
Dermatomyositis/ inflammatory myopathies		Parvovirus B19 associated aplasia	Systemic lupus erythematosis
Myasthenia gravis		Immune hemolytic anaemia	Streptococcal toxic shock syndrome

Australian Guidelines: Conditions which IVIG has an established therapeutic role as immunoglobulin-replacement therapy

- Acquired hypogammaglobulinaemia secondary to haematological malignancies
- Primary immunodeficiency diseases with antibody deficiency

Conditions which IVIG has an established therapeutic role as immunomodulation therapy

- Chronic inflammatory demyelinating polyneuropathy
- Guillain–Barré syndrome
- Idiopathic (autoimmune) Thrombocytopenic Purpura (ITP) in adults
- Inflammatory myopathies (polymyositis, dermatomyositis, inclusion body myositis)
- Kawasaki disease
- Lambert–Eaton myasthenic syndrome
- Multifocal motor neuropathy
- Myasthenia gravis
- Neonatal haemochromatosis
- Stiff person syndrome

Result of Cochrane review and meta analysis on use of IVIG in severe sepsis and septic shock in critically ill adults

- This meta-analysis demonstrates an overall reduction in mortality with the use of IVIg for the adjunctive treatment of severe sepsis and septic shock in adults. (Alejandria, Cochrane reviews 2013)
- As these results are not entirely confirmatory, this data warrants a well-designed, adequately powered, and transparently reported clinical trial.

Adverse effects

- Immediate complications
  - headache/ chills/ nausea
  - anaphylaxis

- Late complications
  - Transfusion transmitted infections
  - Increase in IgG leading to renal impairment
  - Thromboses – cerebral/ coronary

- **PROBLEMS/BARRIERS OF IVIG USE**

  High cost
  Increasing demand
  Inadequate production
  Need for expertise

- There’s no international consensus that shows the world wide trend of IVIG usage at present compared to the past, but the amount produced and the demand varies with
  - Time
  - Clinical indications
  - Demographics
  - Introduction of alternative therapeutics
  - Associated risks of using blood products

Human Albumin

- Albumin is a protein produced endogenously in the liver which has a half life of approximately 3weeks.
- It's the main protein that contributes to plasma oncotic pressure.
- Albumin is derived using plasma and prepared as human albumin solution which can be used in acute conditions such as burns, shock etc.
- In this case the half life drops to 12-16hours.

Physiological functions of albumin in the plasma

- Vascular
  - Maintenance of oncotic pressure
  - Microvascular intergrity
- Transport of hormones, fatty acids, ions (Magnesium, calcium, copper, zinc), bilirubin, bile salts, drugs (warfarin, diazepam)
- Acid-base balance
- ?Antioxidant
- Anticoagulant

General Uses of Human Albumin

- Human albumin is largely used in following situations
  - For correction of hypoalbuminaemia
  - As a volume expander

- In place of human plasma as an exchange fluid
- Safety vs colloids

Appropriate Clinical Indications of Human Albumin:

- Ascites/ large volume paracentesis
  (decreased circulatory dysfunction, hyponatremia, and mortality)
- Spontaneous bacterial peritonitis
- Hepatorenal syndrome

Plasma Replacement

- Therapeutic plasma exchange except in TTP and in Coagulopathies/high risk of bleeding:

Sometimes Appropriate Indications of Albumin:

Correction of hypoalbuminaemia

Organ Transplantation

Liver Transplantation- post operative control of ascites and peripheral oedema.

Liver Cirrhosis with refractory ascites not responding to Diuretics.

Nephrotic Syndrome

Short term infusion of 20%-25% Human Albumin

In association with Diuretics where serum albumin <2g/dl.

Malnutrition Syndrome

May be useful in patient with Diarrhoea who cannot tolerate enteral nutrition.

Sometimes Appropriate Indications of Human Albumin: Volume Replacement

Haemorrhagic shock- When 1st choice solutions of crystalloids and non protein colloids used at maximum doses.

Major Surgery
>40% Resection of Liver
Extensive Intestinal Resection

Heart Surgery
Last choice of treatment as volume expander

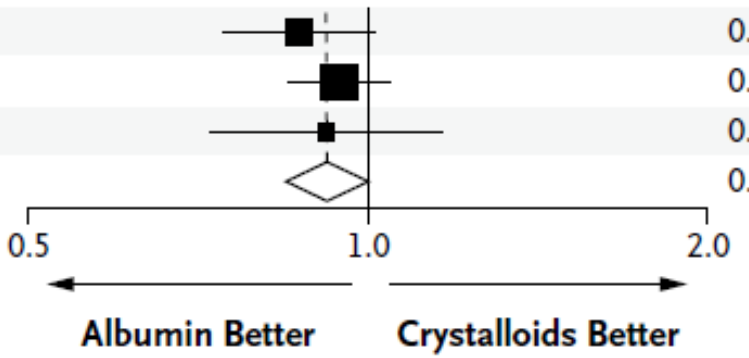
Burns-Shock Resuscitation
(reduces abdominal compartment syndrome/mortality)
(Navidkis et al; Journal of Burn Care and Research)

Albumin for Critically ill and Septic Shock: meta analysis

- Treatment with albumin may increase blood protein level, circulating blood volume and blood pressure when they are abnormally low.
- However, does albumin improve the chances of survival of critically ill patients?: parallels with RBC studies in ICU patients. All cause mortality as end point. No difference compared to colloid/crystalloids but safety established (Patel, BMJ)
- A systematic review and meta analysis: The use of albumin for the resuscitation of patients with septic shock was associated with lower mortality compared with crystalloids or saline. (Xu Critical Care 2014)
- New England Journal of Medicine: colloids/crystalloids
-

NEJM 2014: 3 different trials severe sepsis. Randomised

Trial	Albumin	Crystalloids	Relative Weight	Relative Risk (95% CI)	P Value
	no. of patients who died/total no.		%		
SAFE[2]	185/603	217/615	30.41	0.87 (0.74–1.02)	
ALBIOS[1]	365/888	389/893	54.90	0.94 (0.85–1.05)	
EARSS[3]	96/399	103/393	14.69	0.92 (0.72–1.17)	
All trials	646/1890	709/1901	100.00	0.92 (0.84–1.00)	0.046



When do I use IVIG and Albumin?

- Haem malignancies with low IgG and recurrent infections
- Post allogenenic transplants with recurrent viral infections, esp viral pneumonitis
- ITP
- Haemophagocytosis
- Parvovirus acquired red cell aplasia
- Coagulation inhibitors

When do I use IVIG and Albumin?

- Post transfusion purpura
- Autoimmune Haemolytic Anaemia
- Neurological conditions: plasma exchange vs IVIG

THANK YOU

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