Immune Globulins
728-655

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Learning Objectives

- Discuss the uses of immune globulin for the prevention and treatment of infectious diseases
- Manage adverse events associated with the use of immune globulins
- Anticipate the effects of immune globulins on vaccination
- Evaluate the therapeutic uses of immune globulin for autoimmune diseases, other conditions, and immunodeficiencies

Reading Assignment

Pharmacotherapy. A Pathophysiologic Approach, 11th edition. Chapter 142 Vaccines, Toxoids and Other Immunobiologics. pp 2138-39.

UWHC Criteria for Use of Intravenous Immune Globulin (The 2016 document is the most current version. Please look it over to consider the numerous clinical uses of immune globulin products and see pages 20-21 for administration protocol.)

Reading guide for Chapter 142

Use the learning objectives to guide your reading. The learning objectives have been chosen because of their relevance to immunology pharmacotherapy and are the source of the exam questions.

Consider pages 2138-9 (10th edition 2002-4) essential, but the use of high titer immune globulins is described with its respective vaccine.

Supplemental readings

Gelfand EW. Intravenous immune globulin in autoimmune and inflammatory diseases. N Engl J Med 2012; 367(21): 2015-25

Study questions

What is the function of each class of immune globulin?

For which infectious diseases can immunoglobulin be used for post-exposure prophylaxis?

Why was the dose of pooled immune globulin (Gama STAN S/D) changed for the prevention of hepatitis A? **Updated Dosing Instructions for Immune Globulin (Human) GamaSTAN S/D for Hepatitis A Virus Prophylaxis.** MMWR / September 15, 2017 / 66(36);959–960
https://www.cdc.gov/mmwr/volumes/66/wr/mm6636a5.htm?s_cid=mm6636a5_w

How should adverse effects from IVIG administration be minimized or managed?

Describe the interaction between immune globulin and vaccines.
Describe possible mechanisms for the use of IVIG in the treatment of autoimmune or inflammatory diseases.

TABLE 3-4. Guidelines for administering antibody-containing products[a] and vaccines

Type of administration	Products administered		Recommended minimum interval between doses
Simultaneous (during the same clinic day)	Antibody-containing products and inactivated antigen		Can be administered simultaneously at different anatomic sites or at any time interval between doses
	Antibody-containing products and live antigen		Should not be administered simultaneously.[b] If simultaneous administration of measles-containing vaccine or varicella vaccine is unavoidable, administer at different sites and revaccinate or test for seroconversion after the recommended interval (see Table 3-5)
Nonsimultaneous	**Administered first**	**Administered second**	
	Antibody-containing products	Inactivated antigen	No interval necessary
	Inactivated antigen	Antibody-containing products	No interval necessary
	Antibody-containing products	measles, mumps, rubella vaccine, varicella vaccine, and combined measles, mumps, rubella, varicella vaccine antigens	Dose related[b],[c]

	MMR vaccine, varicella vaccine, and combined measles, mumps, rubella, varicella vaccine antigens	Antibody-containing products	2 weeks[b]

[a] Blood products containing substantial amounts of immune globulin include intramuscular, subcutaneous, and intravenous immune globulin, specific hyperimmune globulin (e.g., hepatitis B immune globulin, tetanus immune globulin, varicella zoster immune globulin, and rabies immune globulin), whole blood, packed red blood cells, plasma, and platelet products.

[b] Yellow fever vaccine; rotavirus vaccine; oral Ty21a typhoid vaccine; live, attenuated influenza vaccine; and zoster vaccine are exceptions to these recommendations. These live, attenuated vaccines can be administered at any time before or after or simultaneously with an antibody-containing product.

[c] The duration of interference of antibody-containing products with the immune response to the measles component of measles-containing vaccine, and possibly varicella vaccine, is dose related (see Table 3-5).

TABLE 3-5. Recommended intervals between administration of antibody-containing products and measles- or varicella-containing vaccine, by product and indication for vaccination

Product/Indication	**Dose (mg IgG/kg) and route[a]**	**Recommended interval before measles- or varicella-containing vaccine[b] administration (months)**
Blood transfusion		
RBCs, washed	10 mL/kg, negligible IgG/kg IV	None
RBCs, adenine-saline added	10 mL/kg (10 mg IgG/kg) IV	3
Packed RBCs (hematocrit 65%)[c]	10 mL/kg (60 mg IgG/kg) IV	6
Whole blood (hematocrit 35%-50%)[c]	10 mL/kg (80-100 mg IgG/kg) IV	6
Plasma/platelet products	10 mL/kg (160 mg IgG/kg) IV	7
Botulinum Immune Globulin Intravenous (Human)	1.5 mL/kg (75 mg IgG/kg) IV	6

Cytomegalovirus IGIV	150 mg/kg maximum	6
Hepatitis A IG		
Contact prophylaxis	0.02 mL/kg (3.3 mg IgG/kg) IM	3
International travel, <3 month stay	0.02 mL/kg (3.3 mg IgG/kg) IM	3
International travel, ≥3 month stay	0.06 mL/kg (10 mg IgG/kg) IM	3
Hepatitis B IG	0.06 mL/kg (10 mg IgG/kg) IM	3
IGIV		
Replacement therapy for immune deficiencies[d]	300-400 mg/kg IV[d]	8
Immune thrombocytopenic purpura treatment	400 mg/kg IV	8
Postexposure varicella prophylaxis[e]	400 mg/kg IV	8
Postexposure measles prophylaxis for immunocompromised contacts	400 mg/kg IV	8
Immune thrombocytopenic purpura treatment	1000 mg/kg IV	10
Kawasaki disease	2 g/kg IV	11
Measles prophylaxis IG		
Standard (i.e., nonimmunocompromised) contact	0.50 mL/kg (80 mg IgG/kg) IM	6
Monoclonal antibody to respiratory syncytial virus F protein (e.g., Synagis [MedImmune])[f]	15 mg/kg IM	None
Rabies IG	20 IU/kg (22 mg IgG/kg) IM	4

Tetanus IG	250 units (10 mg IgG/kg) IM	3
Varicella IG	125 units/10 kg (60-200 mg IgG/kg) IM, maximum 625 units	5

Abbreviations: HIV = human immunodeficiency virus; IG = immune globulin; IgG = immune globulin G; IGIV = intravenous immune globulin; mg IgG/kg = milligrams of immune globulin G per kilogram of body weight; IM = intramuscular; IV = intravenous; RBCs = red blood cells.

[a] This table is not intended for determining the correct indications and dosages for using antibody-containing products. Unvaccinated persons might not be protected fully against measles during the entire recommended interval, and additional doses of IG or measles vaccine might be indicated after measles exposure. Concentrations of measles antibody in an IG preparation can vary by manufacturer's lot. Rates of antibody clearance after receipt of an IG preparation also might vary. Recommended intervals are extrapolated from an estimated half-life of 30 days for passively acquired antibody and an observed interference with the immune response to measles vaccine for 5 months after a dose of 80 mg IgG/kg.

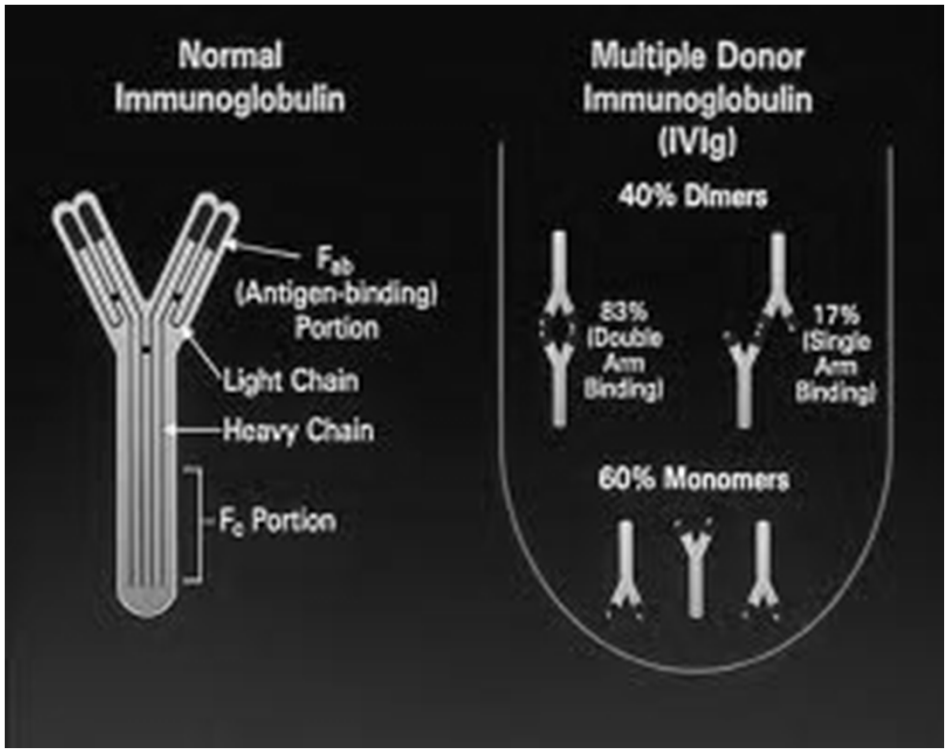
[b] Does not include zoster vaccine. Zoster vaccine may be given with antibody-containing blood products.

[c] Assumes a serum IgG concentration of 16 mg/mL.

[d] Measles vaccination is recommended for children with mild or moderate immunosuppression from HIV infection, and varicella vaccination may be considered for children with mild or moderate immunosuppression, but both are contraindicated for persons with severe immunosuppression from HIV or any other immunosuppressive disorder.

[e] Licensed VariZIG, similar to licensed varicella-zoster IG (VZIG), is a purified human IG preparation made from plasma containing high levels of antivaricella antibodies (IgG).

[f] Contains antibody only to respiratory syncytial virus.


Normal Immunoglobulin
F_{ab} (Antigen-binding) Portion
Light Chain
Heavy Chain
F_c Portion
Multiple Donor Immunoglobulin (IVIg)
40% Dimers
83% (Double Arm Binding)
17% (Single Arm Binding)
60% Monomers

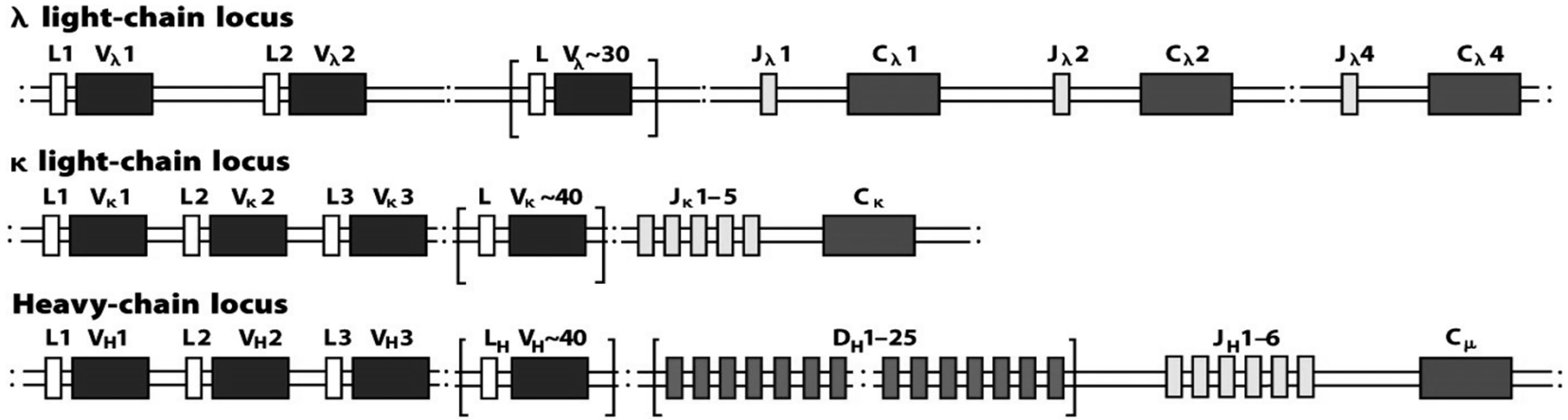


Figure 4-4 Immunobiology, 7ed. (© Garland Science 2008)

V	Variable segments
D	Diversity segments
J	Joining segments
Total possible combinations : ~5×10^{13}	

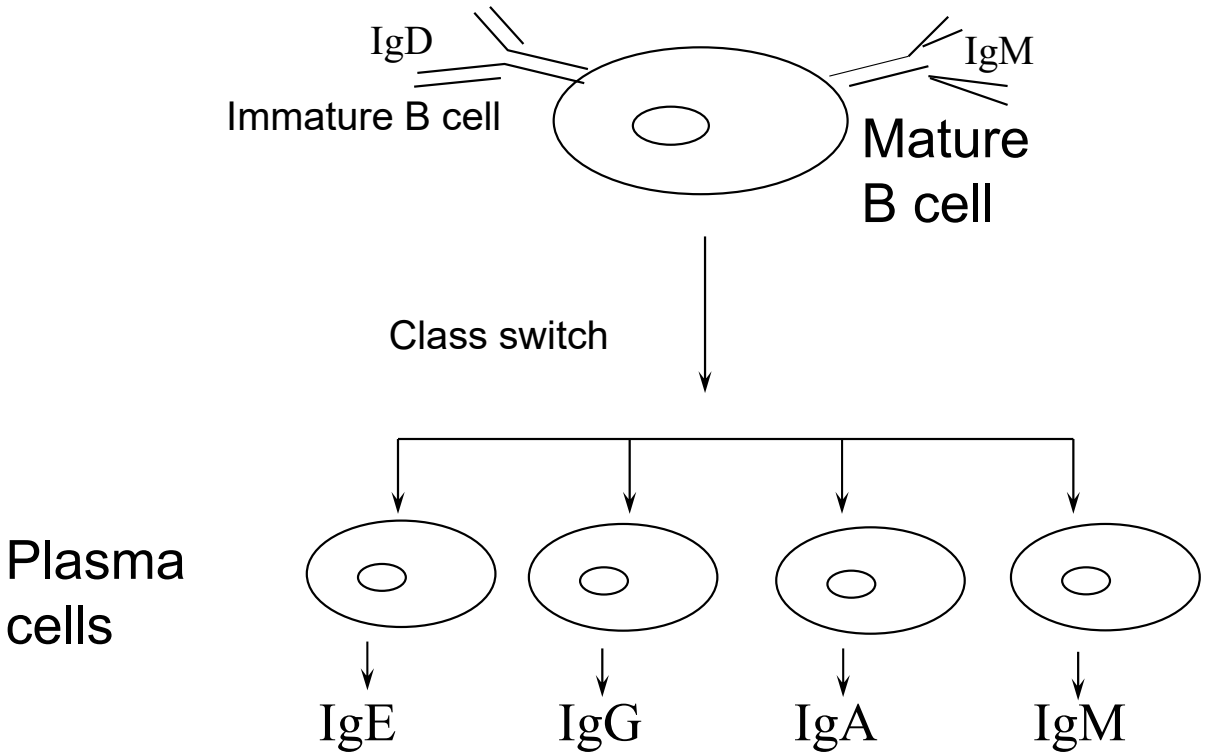
Somatic Recombination

- Used to generate diversity
- Allows generation of antibodies specific to the potential repertoire of antigens
- Controlled hypermutation occurs in activated B cells
    - Generate appropriate antibody for antigen

B cell Selection

- B cell most specific for antigen is chosen for proliferation
- B cells with less or no specificity not selected and undergo apoptosis

B Cell Development



Immune Globulins

- IgA: found in secretions
- IgE: response to parasites; involved in allergy and anaphylaxis
- IgG: found in large amounts in serum; major antibody of secondary response
- IgM: predominant early antibody

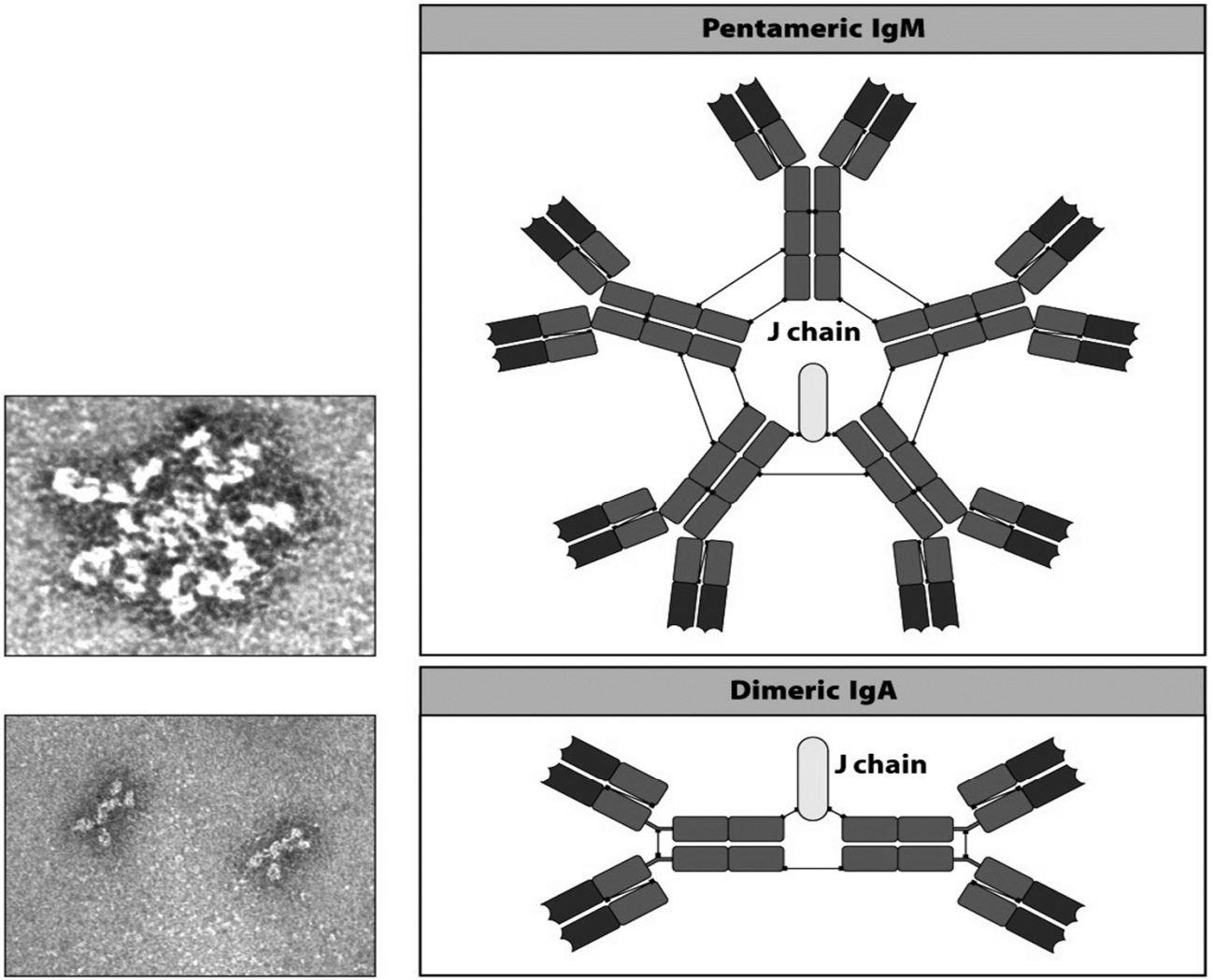
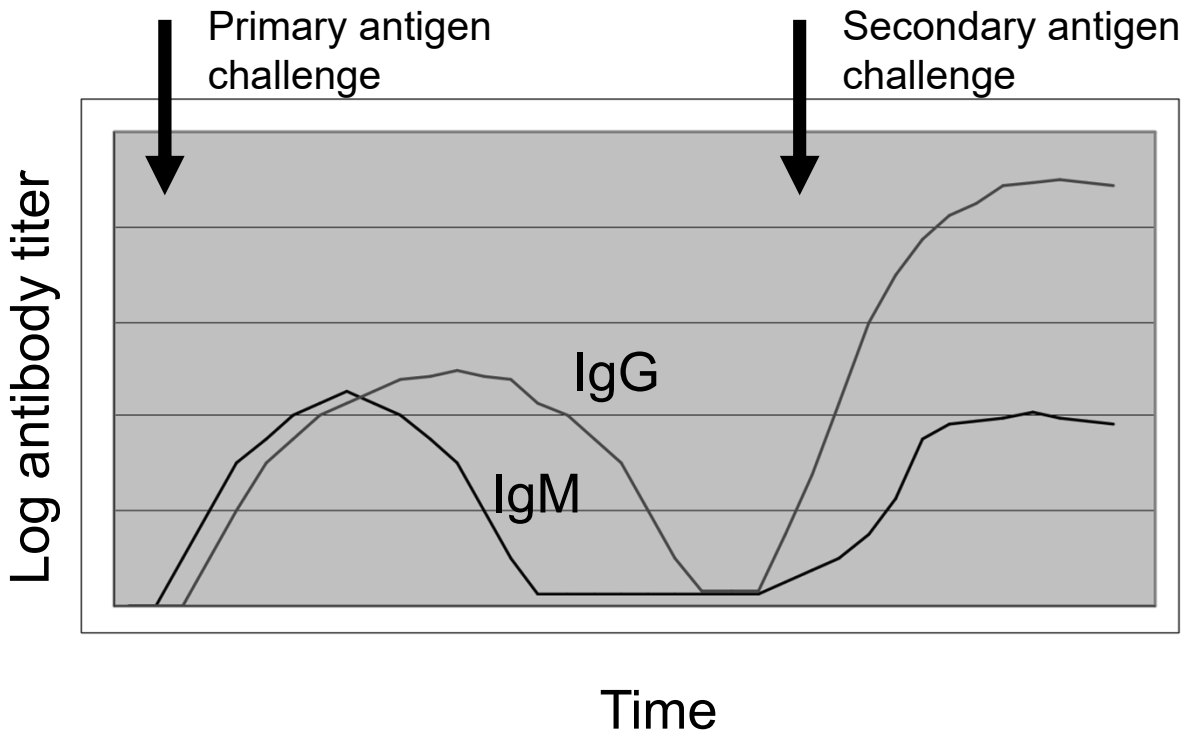


Figure 4-20 Immunobiology, 7ed. (© Garland Science 2008)

Secondary or Booster Response



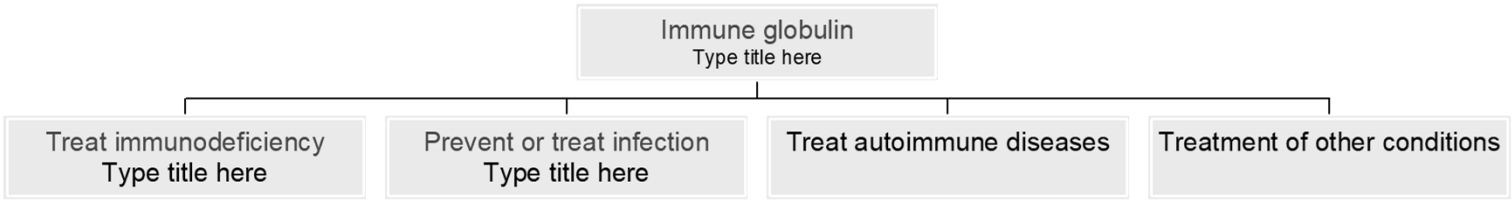
Secondary Antibody Response

- No maturation of IgM response
- Antibodies response after secondary exposure
    - higher affinity
    - appear more quickly
    - persist longer
    - attain higher concentration
    - predominantly IgG

Which of the following classes of antibody provides protection at interfaces with the environment?

a) IgA
b) IgG
c) IgM
d) IgE

Immune Globulin Uses



Immune Globulin Preparations

- Standard preparations probably therapeutically equivalent and interchangeable
- Osmolarity, electrolyte and sugar content, pH differences
- Infection risk very, very small

Adverse Effects

- Mild to moderate headache
  - NSAIDs
- Chills, myalgia, chest discomfort
  - stop infusion for 30 minutes
  - restart infusion at lower rate
- Fatigue, fever, nausea

Adverse Effects

- Increased serum viscosity
  - rare thromboembolic event
- Migraine headache
- Aseptic meningitis
  - infrequently
  - resolves in 24-48 hours

Adverse Effects

- Dermatologic reactions
    - urticaria, pruritis, petechiae
- Severe anaphylactic reactions
    - IgA deficiency with native IgE or IgG antibody that react with IgA in IVIG
- Renal tubular necrosis
    - pre-existing renal disease
    - volume depletion

Spurious Serologic Test Results

- ⇑ ESR
- Hyponatremia
  - related to assay methodology
- Presence of antiviral or antibacterial viral titers

Precautions

- Caution if history of adverse reaction to IVIG
- Epinephrine and other emergency procedures
- Screening for IgA deficiency not routinely recommended

Precautions

- Rate and volume considerations
  - adverse reactions can be alleviated by decreasing rate of administration or volume of infusion
  - repeated severe reactions consider
    - hydrocortisone 1-2 mg/kg prior to infusion
    - diphenhydramine, acetaminophen, aspirin
  - large volume risk for vasomotor or cardiac complications

Vaccine--Antibody Interactions

- Circulating antibody can interfere with response to live vaccines
    - Neutralize vaccine organism before the vaccine pathogen can replicate and induce an immune response in the immunized individual

Immunization Timing

- Maternal antibody interferes with response to live vaccines in infant
- Immunization with live vaccines once child is 12 months old

T.P. is a 22 year old male who had significant contact with a raccoon deemed to have rabies. The patient received rabies immune globulin and began the inactivated rabies vaccine series in the emergency room yesterday. He now presents for follow-up with employee health service. Upon review of his health record including his immunization record, a second dose of a measles-containing vaccine is recommended because he is a healthcare worker. Which of the following would you recommend?

a) Administer an MMR vaccine now
b) Administer the MMR vaccine in 4 weeks
c) Administer an MMR vaccine in 4 months
d) Administer an MMR vaccine in 6 months

Modes of Passive Immunity

- Transplacental transfer
  - active transport of IgG during last 1-2 months of gestation (weeks 32-40)
  - good protection from some diseases--measles, rubella, tetanus
  - poor protection from some diseases--polio,

Modes of Passive Immunity

- Blood transfusion
    - antibody in virtually all blood products
    - amount of antibody transfer depends on blood product and volume
        - small amount in washed RBCs
        - large amount in plasma, whole blood

Modes of Passive Immunity

- Pooled immune globulin preparations
  - Immune globulin (homologous pooled human antibody)
    - pooled from thousands of donors
    - antibodies to many different antigens
  - High titer immune globulins (homologous human hyperimmune globulins)
    - pooled from donors with high titers of specific antibody
    - prophylaxis for specific diseases

Modes of Passive Immunity

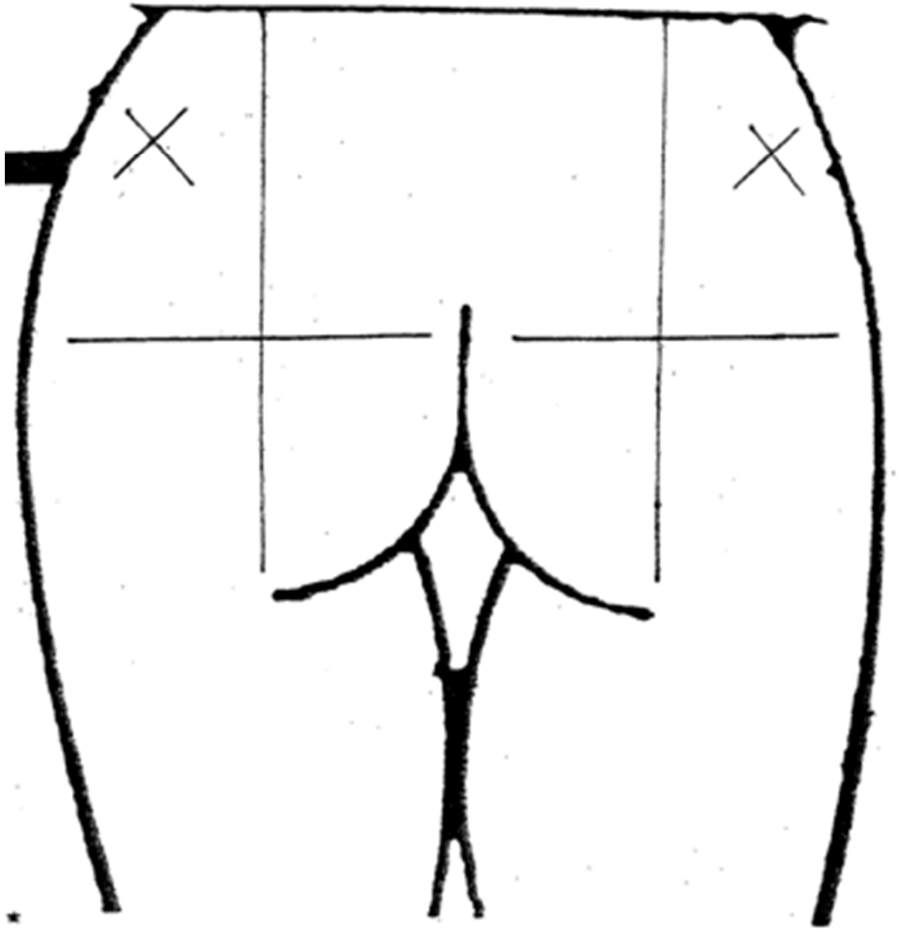
- Pooled immune globulin preparations
    - antitoxin (heterologous hyperimmune serum)
        - derived from hyperimmunized animals
        - contains antibodies against one antigen
        - diphtheria antitoxin
        - botulism antitoxin

Immune Globulin for Infectious Diseases

- Hepatitis A exposure for individuals <12 months
  (if ≥ 12 months. use vaccine if exposed <14 days; if ≥40 years, vaccinate but may also use immune globulin)
- NonA/nonB hepatitis exposure
- Measles
- Varicella zoster exposure (when VZIG not available)
- Low birth weight infants (<1500 g)

Administration Considerations

- Dose differs with infection
- Administered intramuscularly
    - Upper outer quadrant of gluteal region
    - Divide and inject into other muscles if dose >10 ml



Immunodeficiency

- Antibody deficiency
- Combined immune deficiencies
- Intravenous administration
    - average dose 200-400 mg/kg every month

Prevention of Infection

- Passive immunity
- Transfer of immunity produced by one human or animal to another
- Intramuscular or intravenous routes of administration

Cytomegalovirus Immune Globulin

- Alpha herpes virus that causes asymptomatic or mild disease in healthy but serious disease (retinitis, pneumonia, gastrointestinal, hepatitis) in immunocompromised
- Pooled from donors with high antibody titers to CMV
- Used to prevent CMV infection in seronegative recipients of organs from seropositive donors

Hepatitis B Immune Globulin

- Perinatal exposure
    - infants born to mothers who are hepatitis B carriers
    - given within 12 hours of birth
    - start vaccine series at the same time

Hepatitis B Immune Globulin

Type of exposure	Immunoprophylaxis
Sexual contact-acute infection	HBIG + vaccination
Sexual contact-chronic carrier	Vaccination
Household contact-acute infection, known exposure	HBIG + vaccination
Inadvertent percutaneous/ permucosal	Vaccination +/- HBIG

Tetanus Immune Globulin

	Wound Management			
	Clean, minor		**All other**	
Vaccination history	**Td**	**TIG**	**Td**	**TIG**
Unknown or <3 doses	Yes	No	Yes	Yes
3+doses	No*	No	No**	No

*Yes if >10 years since last dose

**Yes if >5 years since last dose

Rabies Immune Globulin

- Used with rabies vaccine for postexposure prophylaxis
- Dose 20 IU/kg
    - half infiltrated around wound
    - half given IM

Which of the following infections is pooled human immune globulin useful in preventing?

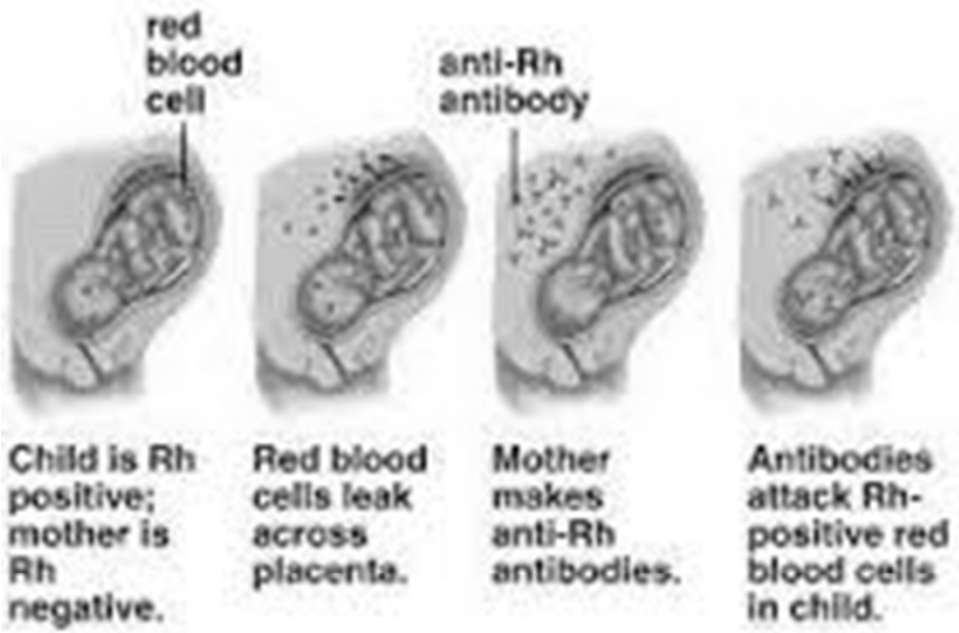
a) Measles
b) Diphtheria
c) Yellow fever
d) Guillain-Barre

Rhesus System Antigens

- Antigens
  - C or c
  - D or d
  - E or e
- RhD much stronger reaction and clinically important
- RhD- individuals lack locus

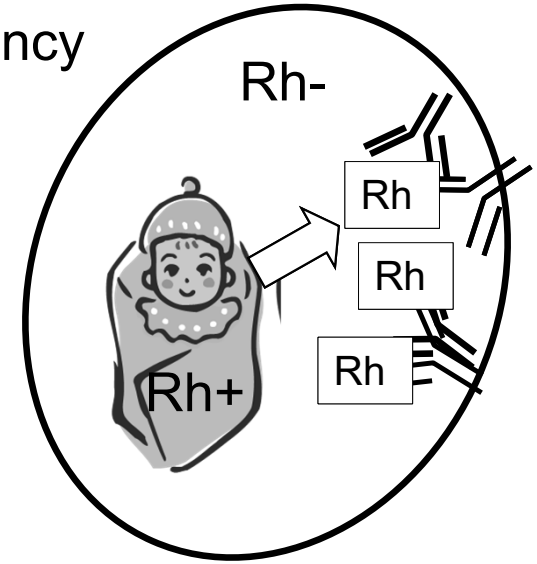
Haemolytic Disease of Newborn

- Occurs when mother is sensitized to RhD on fetal erythrocytes
- Erythrocytes from RhD+ fetus leak to maternal circulation
- Anti-RhD antibodies produced
- Anti-RhD antibodies cross placenta in subsequent pregnancies lysing fetal RhD+ erythrocytes


red blood cell
anti-Rh antibody
Child is Rh positive; mother is Rh negative.
Red blood cells leak across placenta.
Mother makes anti-Rh antibodies.
Antibodies attack Rh-positive red blood cells in child.

Schematic of Rh Sensitization

First pregnancy



Fetal antigen leaks across placenta

Mother mounts antibody response to Rh

Administer antiRh Ab to remove antigens before mother mounts response

Treatment of Rh Incompatibility

- Administration of preformed anti-RhD antibodies
- Eliminates fetal RhD+ erythrocytes that leak into maternal circulation
- Mother does not become sensitized

Rh_o Immune Globulin

- Prepared from plasma or serum of adults with high titers of antibody to RhD
- Microdose sufficient to neutralize 2.5 ml packed red blood cells or 5 ml whole blood
- Standard dose sufficient to neutralize 15 ml packed red blood cells
- Administered intramuscularly

Rh_o Immune Globulin Use

- Full term delivery
  - Standard dose at approximately 28 weeks
  - Standard dose within 72 hours of delivery
- Termination of pregnancy (miscarriage, ectopic pregnancy, abortion)
  - Microdose within 72 hours up to 13 weeks gestation
  - Standard dose within 72 hours after 13 weeks gestation
- Consider with amniocentesis or abdominal trauma during pregnancy

IVIG

- Labeled indications
  - chronic lymphocytic leukemia
  - Kawasaki syndrome
  - immune thrombocytopenia purpura (formerly known as idiopathic thrombocytopenia purpura)

Off-Label Uses of IVIG

- Guillain-Barre syndrome
    - equivalent alternative to plasma exchange
- Chronic inflammatory demyelating polyneuropathy
    - equivalent alternative to plasma exchange

Off-Label Uses of IVIG

- Multiple other conditions when standard treatment fails, not tolerated, or contraindicated
    - myasthenia gravis -premature infants ID
    - polymyositis -dermatomyositis
    - SLE -vasculitis

Table 2. **Potential Antiinflammatory and Immunomodulatory Activities of IgG.***

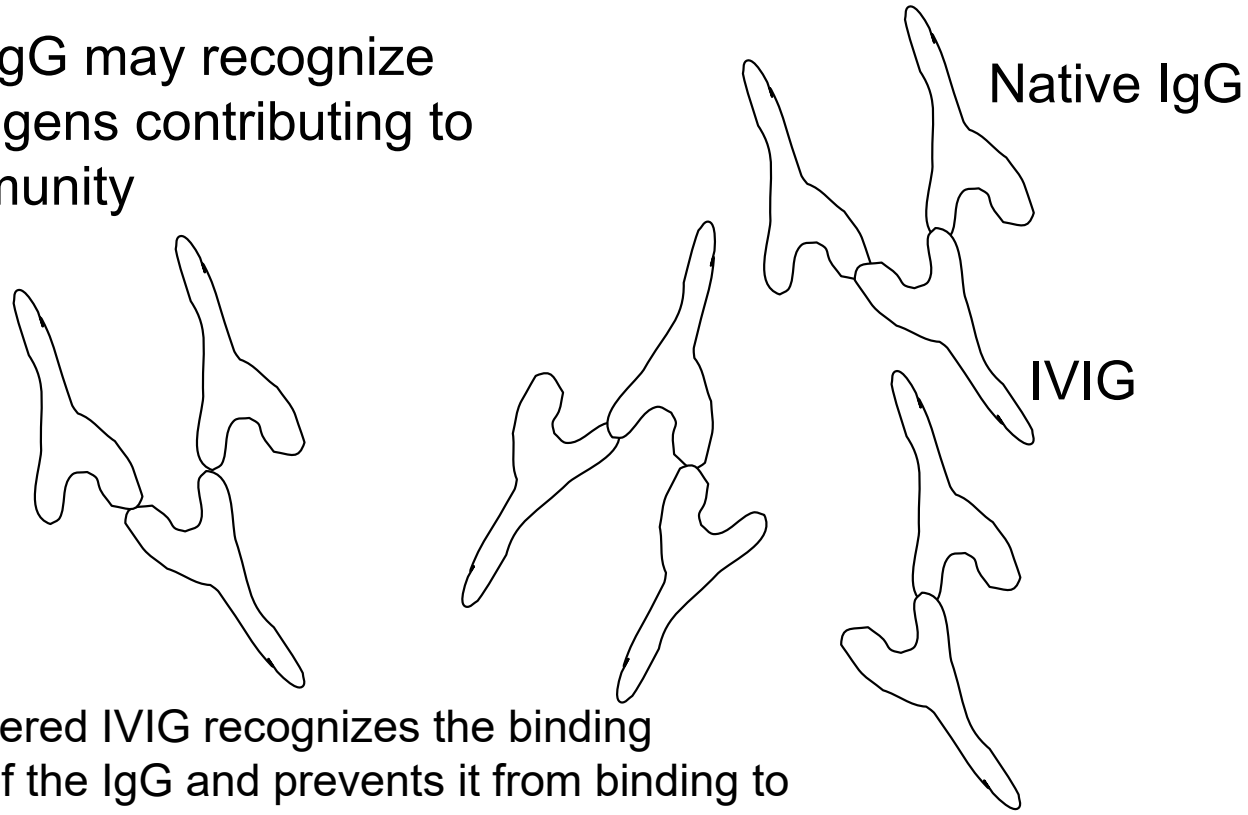
Fab-mediated activities
Suppression or neutralization of autoantibodies
Suppression or neutralization of cytokines
Neutralization of activated complement components
Restoration of idiotypic–anti-idiotypic networks
Blockade of leukocyte-adhesion-molecule binding
Targeting of specific immune cell–surface receptors
Modulation of maturation and function of dendritic cells
Fc-dependent activities
Blockade of the FcRn
Blockade of activating FcγR
Up-regulation of inhibitory FcγRIIB
Immunomodulation by sialylated IgG

* Fab denotes antigen-binding fragment, Fc crystallizable fragment, FcγR receptor for the Fc portion of IgG, and FcRn neonatal Fc receptor.

NEJM 2012

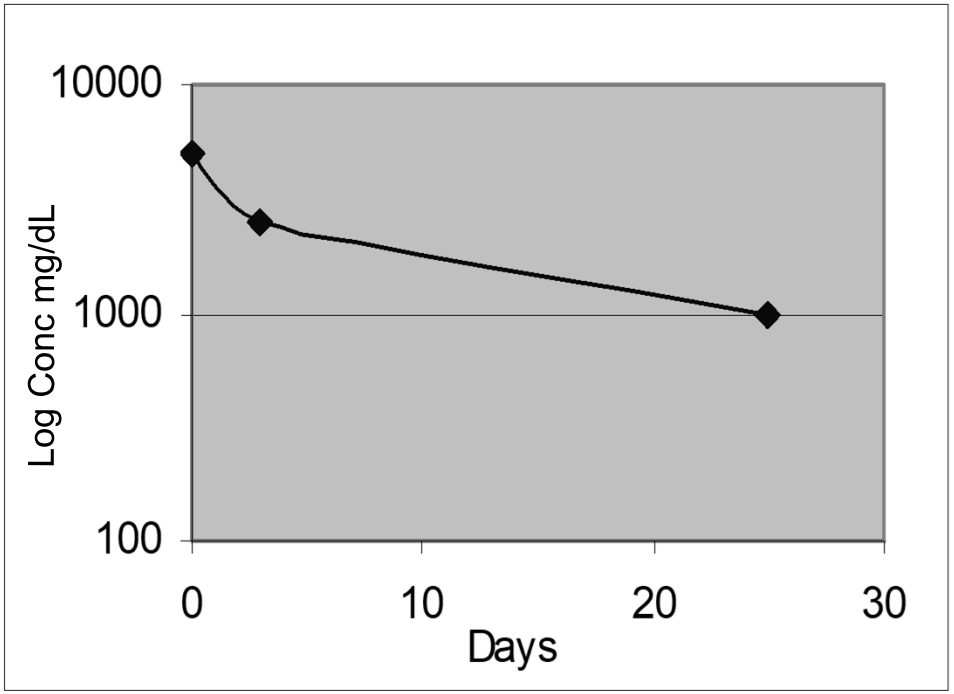
Antiidiotype Mechanism

Native IgG may recognize self-antigens contributing to autoimmunity



Administered IVIG recognizes the binding portion of the IgG and prevents it from binding to self-antigens

IgG Catabolism Mechanism



Chronic Lymphocytic Leukemia

- IVIG as prophylaxis in patients who have had a serious bacterial infection
- Dose 400 mg/kg every 4 weeks

Kawasaki Disease

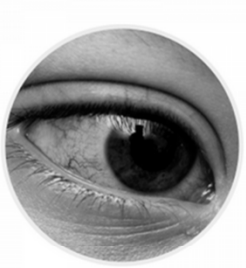
- Febrile, exanthematous multisystem illness
- Predominantly in children 2- 5 years of age
    - 10-32/100,000 children
    - More common in Asian children
    - Winter-early spring predominance
- Characteristic features
    - conjunctival injection
    - erythematous mucous membranes, cracked lips
    - erythematous rash
    - induration, erythema of hands and soles
    - usually solitary enlarged cervical lymph node

Kawasaki Disease Foundation

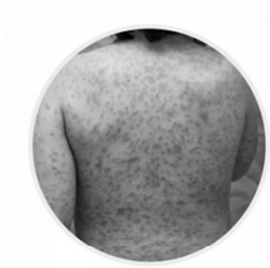
ABOUT KD ABOUT US TAKE ACTION KDF SHOP DONATE

The Symptoms of Kawasaki Disease

Bloodshot Eyes



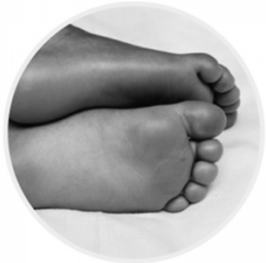
Rash



Strawberry Tongue and Red, Cracked Lips

Swollen Lymph Node in Neck

Red Palms/Soles and Swollen Hands/Feet



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Kawasaki Disease

- Coronary aneurysm develops in 20% of untreated patients
- Other arterial aneurysms may occur
- Coronary dilation may regress
    - not always normal
    - stenosis
- Mortality from myocardial infarction
    - <0.1% in United States

Kawasaki Disease

- Treatment
  - aspirin
    - 80-100 mg/kg/day during fever
    - decrease to 3-5 mg/kg/day after fever controlled
  - high dose IVIG
    - 2 gm/kg

Immune Thrombocytopenia Purpura

- Thrombocytopenia due to accelerated destruction of platelets
- Antiplatelet antibodies mediate destruction
- Management
    - corticosteroids
    - plasmapheresis
    - IVIG infusions
    - splenectomy

Guillain-Barre Syndrome

- Neurological syndrome characterized by loss of reflexes and symmetric paralysis with recovery
- Immune response directed at myelin sheath of peripheral nerves or axon
- May be a triggering event
    - acute infection
    - vaccination