بسم الله الرحمن الرحیم

IVIG & KIDNEY

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CLINICAL USES FOR IVIG

Immunodeficiency states, both primary and secondary – Examples include inborn errors of immunity affecting antibody production or function, chronic lymphocytic leukemia (CLL), multiple myeloma, reduced immune function following hematopoietic stem cell transplantation, and states of severe protein loss.

Neuroimmunologic disorders – Examples include chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy, Guillain-Barré syndrome, and myasthenia gravis.

Autoimmune/inflammatory conditions – Examples include (ITP), autoimmune hemolytic anemia (AIHA), autoimmune neutropenia, acquired von Willebrand syndrome (aVWS), Kawasaki disease, and multisystem inflammatory disease in children (MIS-C) associated with coronavirus disease 2019 (COVID-19).

Infections and infection-related disorders – Examples include chronic parvovirus infection complicated by anemia, toxic shock syndrome, and measles postexposure prophylaxis (if the patient is immunocompromised or nonimmune).

Alloimmune processes – Examples include hemolytic disease of the fetus and newborn (HDFN), post-transfusion purpura, antibody-mediated organ transplant rejection, and hyperhemolytic crisis in individuals with sickle cell disease who have received transfusions

FDA indications for IVIG

IVIG is approved by the FDA for six indications:

1-The treatment of primary immunodeficiencies

2-The prevention and control of bleeding in ITP

3-The prevention of coronary artery aneurysms in Kawasaki disease

4-The prevention of infections and graft-versus-host disease in adult bone marrow transplant patients

5-The prevention of infections in chronic B-cell lymphocytic leukemia

6-The prevention of infections and reduction of hospitalization time in pediatric patients with HIV infection

Off-label uses of IVIG

Neurologic and neurocognitive disorders

Solid-organ transplantation

Infection-related diseases

Dermatologic disorders

Recurrent spontaneous abortion

Vasculitis & SLE

GN

Adverse effect of IVIG

Incidence and risk factors:

-Adverse reactions are reported to occur in 5 to 15 percent of all IVIG infusions and affect 20 to 50 percent of individuals receiving IVIG

->50% reactions occur in the immediate period during or within a few hours of the infusion

-The risk of adverse reactions generally correlates with the dose of IVIG within each course and the rate of infusion

-Most adverse reactions are mild, transient, reversible events such as headache, chills, or flushing.

-Potentially serious reactions occur in 2 to 6 percent of patients

Adverse effect of IVIG

Classification of reaction types:

1- Severity

2-Affected organ system

3-Timing of onset

4-Mechanism

Adverse effect of IVIG

STRATEGIES FOR REDUCING ADVERSE EVENTS

Precautions in all patients

- Therapeutic immunoglobulins should only be given for appropriate indications.
- Administration by the subcutaneous route may reduce the risk of some reactions.
- Patients should be adequately hydrated prior to starting the infusions.
- Slow infusion rates, with gradual stepwise increases, are suggested for new patients or when products are changed.
- Once a product has been established to be safe and effective for a given patient, substitutions of other products should be avoided.
- Patients or designated providers should keep a record of all lots of IVIG and any other blood products received, in case a "look back" is ordered.

Adverse effect of IVIG

STRATEGIES FOR REDUCING ADVERSE EVENTS

Precautions in specific populations

●Patients with a suspected bacterial infection should receive antibiotic therapy before the IVIG infusion to reduce the risk of an excessive inflammatory reaction.

●Patients who develop anaphylaxis and who have very low or undetectable IgA levels (<5 to 7 mg/dL) and IgE anti-IgA antibodies require special attention and should switch to subcutaneous immune globulin (SCIG) or receive a product with low IgA; premedications may also be appropriate.

●Patients who are prone to headaches or have a history of migraine are at increased risk for headaches with infusion and can take a nonsteroidal antiinflammatory drug (NSAID) or acetaminophen prior to, or at the time of, IVIG infusion.

●Patients at increased risk of thromboembolic complications, or those who have had prior thromboembolic complications, may benefit from additional preventive measures including preinfusion hydration and avoidance of prolonged immobility.

●Patients at increased risk of acute kidney injury or those with underlying chronic kidney disease may be given intravenous fluids before beginning the IVIG infusion to avoid hyperviscosity.

Adverse effect of IVIG

ANAPHYLAXIS AND ANAPHYLAXIS-LIKE REACTIONS

OTHER IMMEDIATE REACTION

DELAYED REACTIONS

LATE REACTIONS

Adverse effect of IVIG

ANAPHYLAXIS AND ANAPHYLAXIS-LIKE REACTIONS

- **True or suspected anaphylaxis** – True or suspected anaphylaxis with hypotension and/or respiratory compromise is a medical emergency and should be treated rapidly with immediate discontinuation of the IVIG infusion and administration of intramuscular epinephrine and other therapies

- **Other allergic and immune reactions** – Urticaria, flushing, pain in the chest or lower back, nausea and/or vomiting, and/or a sense of impending doom or sudden anxiety are usually rate related and often occur midway through an IVIG infusion. Tachycardia and/or tachypnea may also be present.

Adverse effect of IVIG

OTHER IMMEDIATE REACTIONS

Pain or systemic (influenza-like) symptoms

Headache and migraine (acute or delayed)

Volume overload (TACO) — Transfusion-associated circulatory overload (TACO) is a syndrome of pulmonary edema due to volume overload. This is more likely to occur in patients with preexisting cardiac or renal disease

TRALI — Transfusion-related acute lung injury (TRALI) is a transfusion reaction that causes acute respiratory distress; it may initially be challenging to distinguish from TACO, although certain features such as fever or hypotension may be helpful in differentiating TRALI from TACO

Adverse effect of IVIG

Helpful features in distinguishing TRALI and TACO

Helpful features in distinguishing TRALI and TACO

Feature	TRALI	TACO
Body temperature	Fever may be present	Unchanged
Blood pressure	Hypotension may be present	Hypertension may be present
Respiratory symptoms	Acute dyspnea	Acute dyspnea
Neck veins	Unchanged	May be distended
Auscultation	Rales	Rales and S3 may be present
Chest radiograph	Diffuse bilateral infiltrates	Diffuse bilateral infiltrates
Ejection fraction	Normal	Decreased
PAOP	Most often 18 mmHg or less	Greater than 18 mmHg
Pulmonary edema fluid	Exudate	Transudate
Fluid balance	Neutral or negative	Positive
Response to diuretics	**Generally not responsive**	**Significant improvement**
White cell count	Transient leukopenia may be present	Unchanged
BNP or NT-pro-BNP	Within normal limits	Significantly elevated

Adverse effect of IVIG

DELAYED REACTIONS

1-Thromboembolic events

2-Complications affecting the kidney:(AKI),hyponatremia

3-Hematologic complications: hemolysis and neutropenia

LATE REACTIONS

Adverse events that may occur weeks to months after receiving IVIG include:

1-**dermatologic reactions**

2-**impaired vaccination response**

3- and the theoretical (but highly unlikely) risk of an **infectious agent transmitted** from the IVIG product.

Adverse effect of IVIG
Complications affecting the kidney

Prescribing information for all IVIG products includes a Boxed Warning about the risks of:

1-Acute kidney injury (AKI)

2- Osmotic nephrosis

3-Death from kidney dysfunction

4-hyponatremia

Adverse effect of IVIG
Acute kidney injury

-Occur with less than 1 percent of infusions

-Risk factors for AKI from IVIG include:

- Age greater than 65 years
- Preexisting chronic kidney disease (CKD; creatinine clearance <60 mL/min)
- Diabetes mellitus
- Higher doses of IVIG
- Hypovolemia
- Concomitant use of nephrotoxic agents
- Very high titers of rheumatoid factor

Adverse effect of IVIG:Acute kidney injury

- Clinical manifestations :vary from an asymptomatic rise in the plasma creatinine concentration to anuria.

-Spontaneous resolution typically occurs within 4 to 10 days after IVIG is discontinued.

-permanent kidney failure has been reported.

- AKI has mostly occurred with IVIG products containing sucrose and led to the discontinuation of these products, although other stabilizing agents have been implicated as well .

Adverse effect of IVIG:Acute kidney injury

-The pathogenesis is believed to involve an osmotic mechanism, similar to that of "sucrose nephropathy," in which sugar is taken up by tubular cells and the increased solute load causes the cells to become vacuolated, swell, and obstruct the tubules, creating a histopathologic lesion referred to as osmotic nephrosis.

-Additional mechanisms that may apply in some patients :

1- renal heme pigment injury related to hemolysis

2- increased blood viscosity

3- immune complex deposition

Adverse effect of IVIG:Acute kidney injury

Strategies to minimize the risk of AKI :

1- Ensuring adequate hydration prior to starting the infusion

2-Avoiding administration of large doses in a single day;

doses can be divided such that no more than 500 mg/kg is administered per day

Adverse effect of IVIG:Acute kidney injury

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Renal Insufficiency and Failure Associated with Immune Globulin Intravenous Therapy -- United States, 1985-1998

Immune globulin intravenous (IGIV) is a sterile, highly purified immunoglobulin G (IgG) preparation made from pooled human plasma stabilized with glucose, maltose, glycine, sucrose, sorbitol, or albumin and is used as prophylaxis or therapy for various medical disorders. The Food and Drug Administration (FDA) first licensed IGIV in 1981 and has approved its use for six conditions: primary immunodeficiencies, immune-mediated thrombocytopenia, Kawasaki syndrome, recent bone marrow transplantation in patients aged greater than or equal to 20 years, chronic B-cell lymphocytic leukemia, and pediatric human immunodeficiency virus type 1 (HIV-1) infection (Table 1). In clinical practice, IGIV has been known to be used to treat 50-60 unapproved conditions, including acute lymphoblastic leukemia, adult HIV infection, multiple sclerosis, Guillain-Barre syndrome, and chronic inflammatory demyelinating polyneuropathy (1). During June 1985-November 1998, FDA received approximately 120 reports worldwide of renal adverse events (RAEs) (i.e., acute renal failure or insufficiency) following IGIV administration. This report describes the epidemiology of IGIV-associated RAEs in the United States and emphasizes the importance of reviewing indications for IGIV use and implementing precautions during its administration.

In the United States, FDA received 88 reports of cases with clinical and/or laboratory findings consistent with a RAE (i.e., increased serum creatinine, oliguria, and acute renal failure) as determined by the treating health-care provider after IGIV administration. Among the 88 case-patients, the median age was 60.5 years (range: 3-91 years); 48 (55%)

Adverse effect of IVIG:Acute kidney injury

Renal Insufficiency and Failure Associated with Immune Globulin Intravenous Therapy -- United States, 1985-1998

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-Approved its use for six conditions: primary immunodeficiencies, immune-mediated thrombocytopenia, Kawasaki syndrome, recent bone marrow transplantation in patients aged greater than or equal to 20 years, chronic B-cell lymphocytic leukemia, and pediatric human immunodeficiency virus type 1

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Adverse effect of IVIG:Acute kidney injury

Renal Insufficiency and Failure Associated with Immune Globulin Intravenous Therapy -- United States, 1985-1998

-conditions associated with acute renal failure:35 (65%) were aged greater than 65 years, 30 (56%) had diabetes mellitus, and 14 (26%) had prior renal insufficiency; 32 (59%) case-patients had one of these conditions, 19 (35%) had two, and three (6%) had 3.

-Seventy-nine (90%) case-patients received sucrose-containing IGIV products, seven received IGIV with maltose or glucose, and two received IGIV in which the stabilizer was undetermined

-Approximately 35 (40%) patients had severe symptoms requiring dialysis

-The mean recovery time of renal function, with or without dialysis, was 10 days (range: 2-38 days) after RAE onset;

-13 (15%) of the 88 patients died despite therapy. These patients had severe underlying conditions (i.e., cardiac insufficiency, pneumonia, or systemic lupus erythematosus)

Adverse effect of IVIG:Acute kidney injury

Acute Renal Failure Associated With Immunoglobulin Therapy

Thomas G. Cantú, PharmD, Edward W. Hoehn-Saric, MD, Kristi M. Burgess, PharmD, Lorraine Racusen, MD, and Paul J. Scheel, MD

● **Four cases of acute renal failure induced by intravenous immunoglobulin are presented, and the literature on the subject is reviewed. The clinical course varies from asymptomatic serum creatinine elevation to anuric renal failure occurring within days of the institution of therapy, followed by the rapid recovery of renal function after termination of therapy. The renal histology demonstrates severe tubular vacuolization with cellular swelling and preservation of the brush border. Glomerular endothelial, mesangial, and epithelial cells also may demonstrate swelling and vacuolization. There is no evidence for inflammatory or immune complex-mediated etiologies. The immunoglobulins or carbohydrate additives in the preparations appear to have a unique and reversible effect on the glomerular and tubular cell function.**

INDEX WORDS: Acute renal failure; immunoglobulin; carbohydrate; vacuolization.

IMMUNOGLOBULIN therapy, first used to treat immune deficiencies in 1952, is now being used for a wide variety of disorders. Intravenous immunoglobulins (IVIGs) serve to replace natural deficiencies, such as those accompanying common variable immunodeficiency or chronic lymphocytic leukemia; they modulate the immune system as in the treatment of idiopathic thrombocytopenic purpura, Kawasaki's syndrome, and Guillain-Barŕe syndrome, and they aid in the prophylaxis of certain infections, such as cytomegalovirus, in the transplant population.[1-4] The seven different preparations of IVIGs that are currently licensed for use in the United

noted in the Food and Drug Administration labeling of any of the IVIG products.[16] As a result, many clinicians are unaware of this potential complication. We report four cases of ARF associated with the use of IVIGs, review the current literature, and discuss possible pathophysiologic mechanisms.

PATIENTS AND METHODS

Case No. 1

A 55-year-old man was diagnosed with idiopathic thrombocytopenia. He was treated with corticosteroids and an IVIG (brand administered is not known), which increased his plate-

Adverse effect of IVIG:Acute kidney injury

The renal histology demonstrates :

1-Severe tubular vacuolization with cellular swelling and preservation of the brush border.

2- Glomerular endothelial, mesangial, and epithelial cells also may demonstrate swelling and vacuolization.

3- There is no evidence for inflammatory or immune complex-mediated etiologies.

4- The immunoglobulins or carbohydrate additives in the preparations appear to have a unique and reversible effect on the glomerular and tubular cell function.

Adverse effect of IVIG:Acute kidney injury

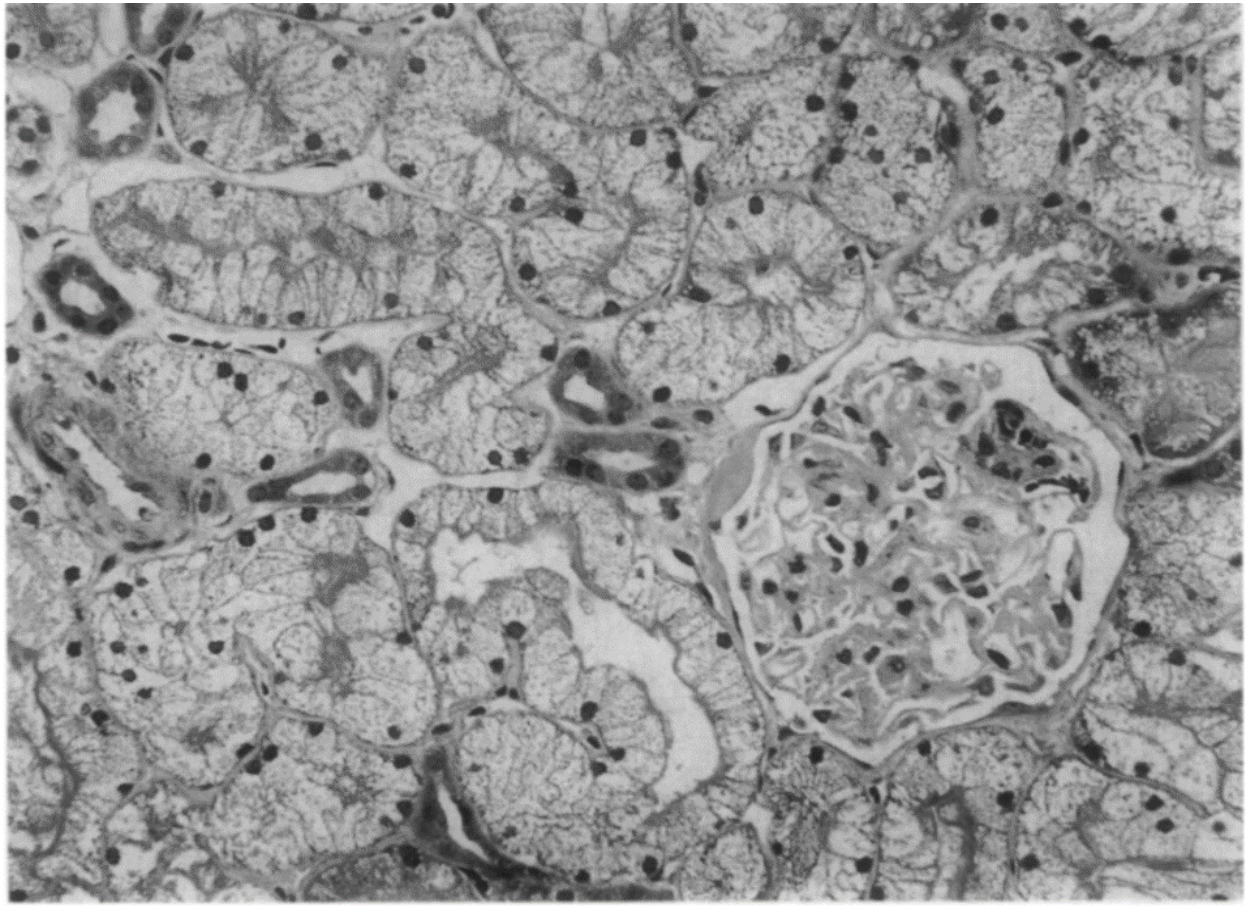


Fig 1. Photomicrograph depicting a glomerulus and tubules from patient no. 3. There is marked vacuolization and edema of the proximal tubules. Note the relative preservation of the brush border. (Hematoxylin-eosin stain; magnification ×280.)

Adverse effect of IVIG:Acute kidney injury

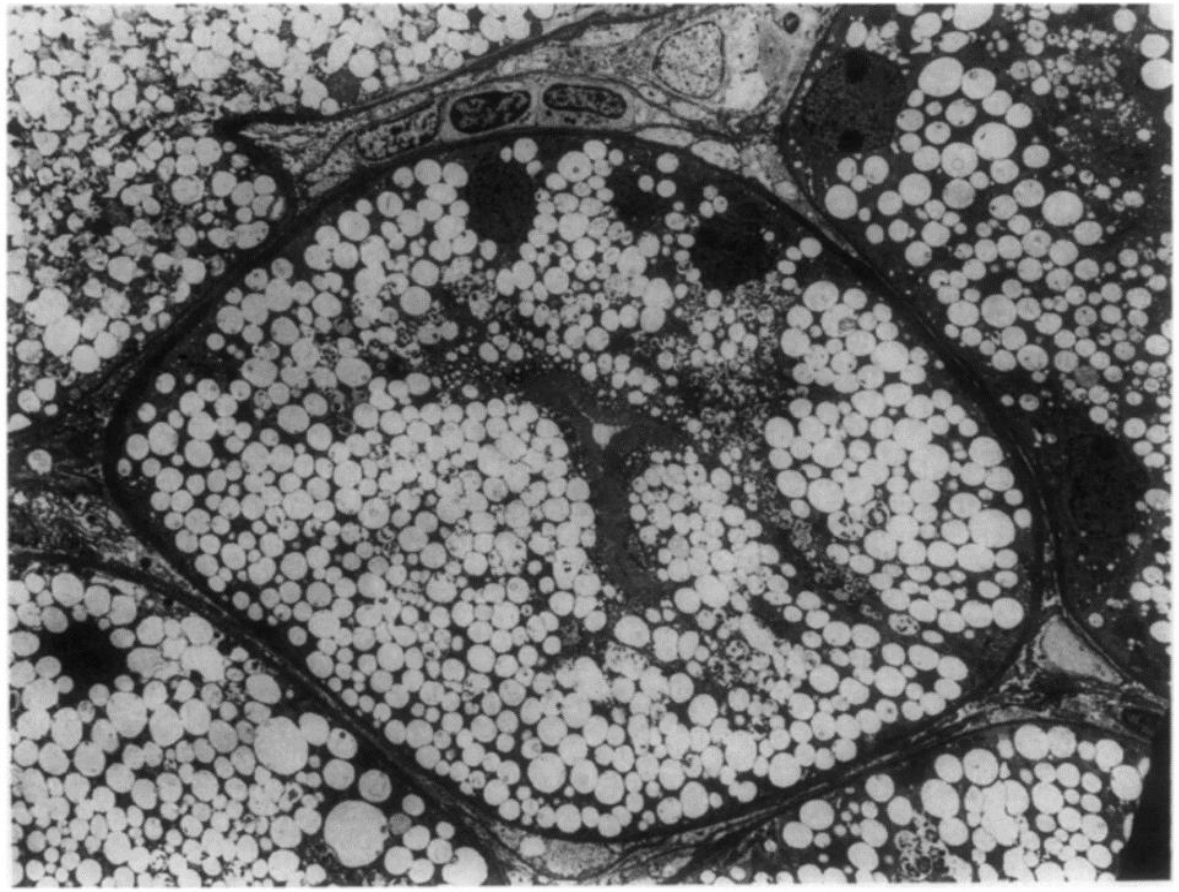


Fig 2. Electron micrograph of a tubule demonstrating the extensive vacuolization throughout the cell with preserved apical brush borders. (Magnification ×1,225.)

Adverse effect of IVIG:Acute kidney injury

Osmotic nephrosis

-A morphological pattern with vacuolization and swelling of the renal proximal tubular cells.

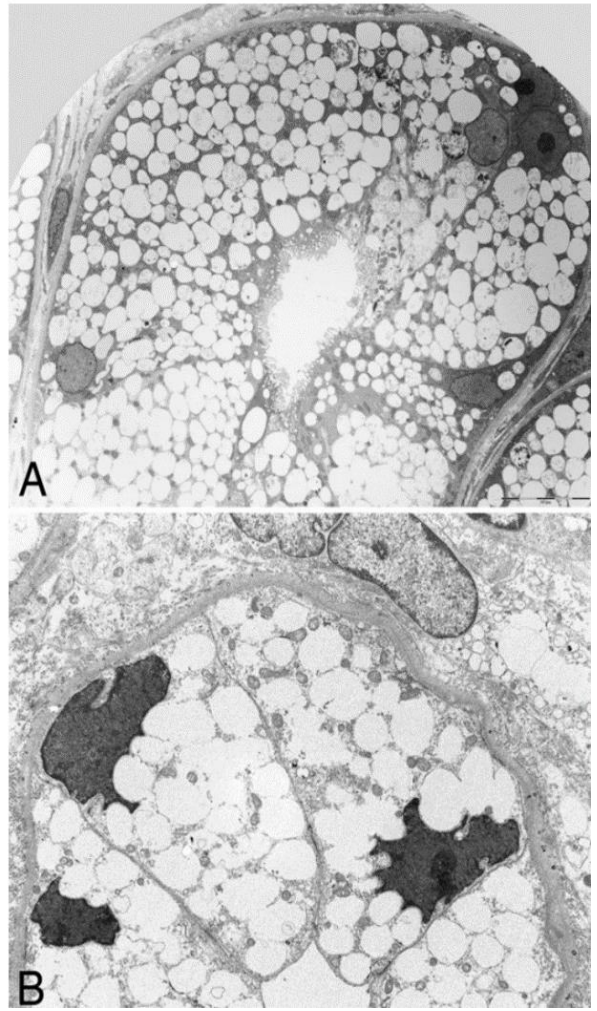
-The term refers to a nonspecific histopathologic finding rather than defining a specific entity.

- Osmotic nephrosis can be induced by many different compounds, such as sucrose, hydroxyethyl starch, dextrans, and contrast media.

- It has a broad clinical spectrum that includes acute kidney injury and chronic kidney failure in rare cases

Adverse effect of IVIG:Acute kidney injury
osmotic nephrosis

electron microscopic picture of osmotic nephrosis in a kidney biopsy specimen. (A, B) Tubular crosssection with seemingly no lumen. Epithelial cells are masssively swollen, cytoplasm is completely filled by vacuoles of about the same size (isometric vacuoles), and nuclei are displaced to the base of the cells and distorted by adjacent vacuoles.



Adverse effect of IVIG:hyponatremia

- Hyponatremia is a rare complication of IVIG that can occur in individuals with underlying CKD or those who develop AKI from the IVIG therapy .

-The mechanism is dilutional and is thought to involve the inability of the kidney to handle the free water load in the setting of an underlying defect in free water excretion.

- Free water comes from the IVIG solution as well as from translocation of water from the intracellular to the extracellular compartment as a result of high concentrations of maltose in one IVIG solution

Adverse effect of IVIG:hyponatremia

-It is important to distinguish true hyponatremia, which is associated with decreased serum osmolality, from pseudohyponatremia, which is a laboratory artifact .

-A clue to pseudohyponatremia is a concomitant normal serum osmolality .

-Distinction between true hyponatremia and pseudohyponatremia using measurement of serum osmolality is presented separately.

Take home message:

1-IVIG :FDA approval:6 condition

offlabel:50-60 condition

2-RAE :Occur with less than 1 percent of infusions

3-Risk factors for AKI from IVIG include:

- Age greater than 65 years
- Preexisting chronic kidney disease (CKD; creatinine clearance <60 mL/min)
- Diabetes mellitus
- Higher doses of IVIG
- Hypovolemia
- Concomitant use of nephrotoxic agents
- Very high titers of rheumatoid factor

Take home message:

Clinical manifestations :

-Vary from an asymptomatic rise in the plasma creatinine concentration to anuria.

-Spontaneous resolution typically occurs within 4 to 10 days after IVIG is discontinue .permanent kidney failure has been reported.

-AKI has mostly occurred with IVIG products containing sucrose .

Strategies to minimize the risk of AKI :

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2-Avoiding administration of large doses in a single day.