PARENTERAL IRON

INDICATIONS:

Cannot tolerate oral iron;
Malabsorbtion of iron because of gastric resection and/or bilroth II operation;
Continue to lose blood at a rate that is too rapid for oral absorption to compensate.

Iron dextran-most experience, highest rate of severe allergic reactions, can give in total-dose infusion.

Iron sucrose-very low rate of severe allergic reactions, test dose not required, more expensive, see monograph for maximum doses per infusion.

Iron gluconate- very low rate of severe allergic reactions, test dose not required, more expensive, extensive data in dialysis patients, see monograph for maximum doses per infusion.

DOSAGE:

Iron to be injected (mg) = [15 - Patient's hemoglobin (g/dL)] x body weight (kg) x 3

**usually 1.5 to 2 grams for most patients

Test dose (test dose prepared by pharmacy usually 25 - 50 mg diluted in 50 mL normal saline) is given first then the entire dose is given diluted into 500 mL to 1 liter of normal saline - given over several hours.

REACTIONS:

Immediate side effects include hypotension, urticaria, headache, nausea, and anaphylactic reactions. Delayed reactions include fever, arthralgias, lymphadenopathy, and myalgia.

Reference: Silverstein SB, Rodgers GM. *Am J Hematol* 2004;76:74 - 8.

PARENTERAL IRON PRODUCTS

IRON DEXTRAN
(INFED, DEXFERRRUM®)

I. MECHANISM OF ACTION

Iron dextran consists of a complex of ferric oxyhydroxide with dextrans of 5000 -7000 daltons. Its use is usually reserved for iron-deficient patients unable to take or intolerant to oral iron preparations. Parenteral iron produces therapeutic responses similar to those of oral iron. One advantage of parenteral iron is that iron stores are rapidly repleted, which may take months to achieve with oral iron therapy. Iron dextran was approved by the FDA prior to 1982.

A) Iron-carbohydrate complex is separated by the reticuloendothelial system.
B) Iron is gradually released into the circulation.
C) Iron combines with transferrin for transport to the liver, spleen, and bone marrow.
D) Iron binds to the bone marrow receptor sites for hemoglobin synthesis.

II. PHARMACOKINETICS

A) Administered intramuscularly or intravenously.
B) 90% of an IM dose is absorbed within 1-3 weeks through two stages involving absorption into the lymphatics.
C) Absorption by intravenous route is quicker.
D) Cellular uptake is 10-20mg/hr.
E) There is no destructive metabolism of iron because it takes place in a closed system.

III. DOSAGE AND ADMINISTRATION

A) Many formulas exist to calculate iron dosing:
- estimate (15-pts hb (g/dL)) x body weight (kg) x3

B) Dose can be given intravenously or intramuscularly.
C) Can be given as a total dose infusion or in divided doses if given intravenously. Intramuscular doses are generally restricted to 100mg. Each ml of iron dextran contains 50ml of elemental iron.
D) A test dose of 25 mg (0.5 ml) of iron dextran should be given by the route and method of administration for which therapeutic doses will be administered. Observe patient for at least 1 hour after test dose administration.
E) Do not mix with other medications.
F) If the intramuscular route is chosen use the Z-track technique of injection to avoid staining of the tissue.
G) FDA pregnancy risk category C.

IV. TOXICITY

A) Anaphylaxis in 0.6%-0.7% of administrations. Less major allergic/hypersensitivity reactions are more common.
B) Hypotension/Hypertension.
C) Bradycardia.
D) Chest pain.
E) Nausea, vomiting and abdominal pain.
F) Arthralgas, myalgas and back pain.
G) Headache and fevers.

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V. CLINICAL MONITORING

A) Hb/Hct
B) Reticulocyte count
C) Ferritin

NOTE: Test dose should be administered prior to dose.

VI. DRUG INTERACTIONS

A) Iron dextran should not be administered with other parenteral iron formulations or iron salts.
B) It would be counterintuitive to administer iron dextran with iron chelating agents.
C) Iron dextran should not be administered with Dimercaprol as it forms toxic-chelates with iron, cadmium, and selenium. These dimercaprol-metal complexes are more toxic than the metal alone, especially to the kidneys.

IRON SUCROSE
(VENOFER®)

I. MECHANISM OF ACTION

Iron sucrose consists of a urib hydroxyide sucrose complex in water. The molecular mass of of iron sucrose is 34,000-64,000 daltons. Its use is usually reserved for iron-deficient patients unable to take or intolerant to oral iron preparations. Parenteral iron produces therapeutic responses similar to those of oral iron. One advantage of parenteral iron is that iron stores are rapidly repleted, which may take months to achieve with oral iron therapy. Iron sucrose was approved by the FDA in November of 2000 and in the treatment of non-dialysis dependent iron deficiency in October 2005.

A) Following IV administration of iron sucrose, the complex of polynuclear iron (III)-hydroxide in sucrose is dissociated into iron and sucrose by the reticuloendothelial system.
B) Iron is gradually released into the circulation.
C) Iron combines with transferrin for transport to the liver, spleen, and bone marrow.
D) Iron binds to the bone marrow receptor sites for hemoglobin synthesis

II. PHARMACOKINETICS

A) Administered intravenously.
B) The sucrose component is eliminated primarily by urinary excretion (75.4% in 24 h).
C) Approximately 5% of the iron is excreted in the urine over 24 hours.
D) The iron component exhibits linear kinetics with an elimination half-life of about 6 hours and a systemic clearance of 1.2 L/h.
E) There is no destructive metabolism of iron because it takes place in a closed system.

III. DOSAGE AND ADMINISTRATION

A) Many formulas exist to calculate iron dosing:
- estimate (15-pts hb (g/dL)) x body weight (kg) x3

B) Dose is given intravenously.
C) Test dose is optional.
D) Doses of 100-200 mg of elemental iron adminstered over 2—5 minutes and repeated 1-3 times weekly until desired dose is reached.
E) Doses of 400-500mg over 2-4 hours have been used, but with increased side effects.
F) FDA pregnancy risk category B.

IV. TOXICITY

A) Anaphylaxis in .0002% of administrations. Less major allergic/hypersensitivity reactions are more common.
B) Hypotension/Hypertension.
C) Pruritis.
D) Chest pain.
E) Nausea, vomiting and abdominal pain.
F) Arthralgas, myalgas and back pain.
G) Headache.

V. CLINICAL MONITORING

A) Hb/Hct
B) Reticulocyte count
C) Ferritin

NOTE: Test dose can be considered, but is not required prior to dose.

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VI. DRUG INTERACTIONS

A) Iron sucrose should not be administered with other parenteral iron formulations or iron salts.
B) It would be counterintuitive to administer iron sucrose with iron chelating agents.
C) Iron sucrose should not be administered with Dimercaprol as it forms toxic-chelates with iron, cadmium, and selenium. These dimercaprol-metal complexes are more toxic than the metal alone, especially to the kidneys.
D) Concurrent use of chloramphenicol with iron sucrose can antagonize the hematopoietic response to iron.

SODIUM FERRIC GLUCONATE
(FERRLECIT®)

I. MECHANISM OF ACTION

The molecular weight is of 350,000 daltons. Its use is usually reserved for iron-deficient patients unable to take or intolerant to oral iron preparations. Parenteral iron produces therapeutic responses similar to those of oral iron. One advantage of parenteral iron is that iron stores are rapidly repleted, which may take months to achieve with oral iron therapy. Sodium ferric gluconate was approved by the FDA in 1989.

A) Iron-carbohydrate complex is separated by the reticuloendothelial system.
B) Iron is gradually released into the circulation.
C) Iron combines with transferrin for transport to the liver, spleen, and bone marrow.
D) Iron binds to the bone marrow receptor sites for hemoglobin synthesis.

II. PHARMACOKINETICS

A) Administered intramuscularly.
B) The terminal elimination half-life is approximately 1 hour.
C) 80% of drug bound iron was delivered to transferrin as a mononuclear ionic iron species within 24 hours of administration.
D) There is no destructive metabolism of iron because it takes place in a closed system.

III. DOSAGE AND ADMINISTRATION

A) Many formulas exist to calculate iron dosing:
- estimate (15-pts hb (g/dL)) x body weight (kg) x3

B) Dose is given intravenously.
C) Typically given in divided doses of 125mg over 10 minutes repeated until desired dose is reached.
D) A test dose of 25 mg (0.5 ml) is generally not required.
E) Do not mix with other medications.
F) If the intramuscular route is chosen use the Z-track technique of injection to avoid staining of the tissue.
G) FDA pregnancy risk category B.

IV. TOXICITY

A) Anaphylaxis in 0.4% of administrations. Less major allergic/hypersensitivity reactions are more common.
B) Hypotension/Hypertension.
C) Bradycardia.
D) Chest pain.
E) Nausea, vomiting and abdominal pain.
F) Arthralgas, myalgas and back pain.
G) Headache and fevers.

V. CLINICAL MONITORING

A) Hb/Hct
B) Reticulocyte count
C) Ferritin

NOTE: Test dose can be considered, but is not required prior to dose.

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VI. DRUG INTERACTIONS

A) Iron gluconate should not be administered with other parenteral iron formulations or iron salts.
B) It would be counterintuitive to administer iron gluconate with iron chelating agents.
C) Iron gluconate should not be administered with Dimercaprol as it forms toxic-chelates with iron, cadmium, and selenium. These dimercaprol-metal complexes are more toxic than the metal alone, especially to the kidneys.
D) Higher adverse event rate was seen in patients receiving concomitant ACE inhibitors.

DEFERASIROX
(EXJADE®)

Deferasirox is the first in a new class of tridentate, oral, iron-chelating agents used in the treatment of chronic iron overload secondary to multiple RBC transfusions (i.e., transfusional iron overload). Deferasirox has been developed as an alternative to deferoxamine, the standard treatment of chronic iron overload which is administered parenterally. Deferasirox was approved by the FDA in November 2005.

I. MECHANISM OF ACTION

Deferasirox is an orally active iron chelator that binds selectively to Fe^{3+}. It is a tridentate ligand that requires two molecules of itself to form a stable complex with each iron atom. One oral dose of deferasirox appears to be four to five times more effective than parenterally administered deferoxamine in promoting the excretion of chelatable iron from hepatocellular iron stores. Deferasirox is highly selective for iron, while it does not appear to promote dietary absorption of iron.

II. PHARMACOKINETICS

A) Deferasirox is administered orally.
B) Maximum plasma concentration (Cmax) is reached in about 1.5 to 4 hours.
C) Deferasirox tablets for oral suspension have an absolute bioavailability of 70%.
D) Deferasirox should be taken on an empty stomach 30 minutes before eating.
E) It is highly (~99%) protein bound, binding almost exclusively to serum albumin.
F) The main metabolic pathway for deferasirox is glucuronidation, with subsequent biliary excretion.
G) The mean elimination half-life ranged from 8 to 16 hours following oral administration.
H) Deferasirox has not been studied in patients with renal or hepatic impairment.
I) The pharmacokinetics of deferasirox have not been studied in geriatric patients (65 years of age and older).

III. DOSAGE AND ADMINISTRATION

A) Oral dosage (125 mg, 250mg, and 500 mg tablets for suspension):
Adults and children > 2 years: 20 mg/kg PO daily; calculate dose to the nearest whole tablet mg strength. Once treatment is initiated, monitor serum ferritin concentrations monthly. *Children < 2 years*: Safety and efficacy have not been established.
B) For maintenance therapy:
Oral dosage (125 mg, 250mg, and 500 mg tablets for suspension):
Adults and children > 2 years: Following initial dosing, adjust dose every 3—6 months in increments 5 to 10 mg/kg (to the nearest whole tablet mg strength) to max of 30mg/kg based on serum ferritin concentrations. If the serum ferritin consistently falls below 500 mcg/L, consider temporarily interrupting therapy.
C) Use caution with renal impairment. Elevated serum creatinine may be expected during treatment, and dose reduction or treatment interruption should be considered. Dose adjustments can be made in increments of 5—10 mg/kg/day.
D) Use caution with hepatic impairment. Specific guidelines for dosage adjustments in hepatic impairment are not available. Dose modifications should be considered for severe or persistent elevations.
E) Administer on an empty stomach at least 30 minutes before food, at approximately the same time every day. Do not administer with any aluminum-containing antacid products. Completely disperse the tablets in liquid.

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IV. TOXICITY

A) Most common side effects: Diarrhea, nausea/vomiting, abdominal pain.
B) Fever, headache, cough >5%.
C) Erythematous maculopapular rash.
D) Renal and hepatic impairment.
E) Hearing and visual impairment <1%.
F) Cytopenias- including agranulocytosis, neutropenia, and thrombocytopenia have been reported. The relationship of cytopenias to deferasirox is uncertain; in clinical trials most of the patients in whom the cytopenias were reported had preexisting hematologic disorders.

V. CLINICAL MONITORING

A) Audiometry- prior to initiation and annually
B) Ferritin
C) LFTs
D) Ophthalmologic exam with intraocular pressure and evaluation for lens opacities- prior to initiation and annually thereafter.
E) Serum creatinine/BUN
F) Serum iron
G) Urinalysis for prtoeinuria
H) Urine osmolality

VI. INTERACTIONS

UGT1A1 is the primary enzyme involved in glucuronidation of deferasirox. If a concomitantly administered drug undergoes selective metabolism by UGT1A1, competition for drug metabolism will exist, possibly resulting in the reduced clearance of deferasirox. Although the potential benefits of combination iron chelation therapy have been mentioned in the literature, it is currently recommended that deferasirox not be combined with other iron chelator therapies as the safety of such combinations has not been established. Because deferasirox may bind to aluminum instead of iron, aluminum containing antacids should not be administered concurrently in order to avoid a possible decreased efficacy of either therapy.

IMMUNOGLOBULIN DOSING (IVIG)

ITP

IVIG	1000 mg/kg/day	IV	Days 1 and 2
	OR		
IVIG	400 mg/kg/day*	IV	Days 1 – 5

*Administer as protracted infusion if volume is a concern.

NOTE: Use with caution in renal failure and IgA deficiency

Reference: Psaila B, et al. *Hematol Oncol Clin North Am* 2007;21:743 – 59.

PRIMARY IMMUNODEFICIENCY

IVIG	400 mg/kg	IV	Monthly

Titrate frequency to achieve target IgG levels.

NOTE: Use with caution in renal failure and IgA deficiency

Reference: Yong PF, et al. *Immunol Allergy Clin North Am* 2008;28:367 – 86.

IMMUNE GLOBULIN IV (IVIG)

(CARIMUNE™ | CARIMUNE™ NF | FLEBOGAMMA® | GAMIMUNE® N | GAMMAGARD | GAMMAGARD® S/D | GAMMAR®-P IV | GAMUNEX® | IVEEGAM® | IVEEGAM® EN | OCTAGAM™ | PANGLOBULIN® | PANGLOBULIN® NF | POLYGAM® S/D | SANDOGLOBULIN® | VENOGLOBULIN®-S | VIGAM™)

Immune globulin IV (IVIG) is an intravenous solution composed primarily of heterogenoushuman IgG, with trace amounts of IgA and IgM. IVIG is collected from the venous blood of multiple donors. The amount of each IgG subclass is similar to that of human plasma, although the titers against specific antigens vary among manufacturers. Also, the IVIG products differ in the preparation method, viral inactivation steps, stabilizing agent, osmolality, and IgA content. Thus, the IVIG products are not the same. In March 2000, the FDA established the efficacy criterion for approval of IVIG products as no more than 1 serious infection per patient per year.

I. MECHANISM OF ACTION

The pooled, heterogenous IgG present in IVIG provides a large heterogenous variety of antibodies capable of opsonization and neutralization of many toxins and microbes as well as complement activation. The passive immunity imparted by IVIG is capable of attenuating or preventing infectious diseases or deleterious reactions from toxins, mycoplasma, parasites, bacteria, and viruses. IVIG has been used in many different autoimmune and disease processes. Hematologic indications are the focus of this monograph.

II. PHARMACOKINETICS

A) Peak plasma concentrations occur immediately after infusion.
B) Biphasic decay curve.
C) Within 24 hours, up to 30% of a dose may be removed by catabolism and distribution throughout intravascular (60%) and extravascular (40%) spaces, crosses the placenta (in increasing amounts after 30 weeks of gestation), and may be excreted into milk.
D) The exact fate of IVIG is not well defined, but the serum half-life is that of immune globulin (IgG), approximately 21—29 days. Great interpatient variability exists for the half-life of IgG.

III. DOSAGE AND ADMINISTRATION

A) In the treatment of ITP doses have been up to 2g/kg total administered over 2-5 days. In cases where prompt response is essential administration over 2 days is recommended. In cases where volume overload is a concern administration over 5 days may be preferred.
B) In the treatment of CVID dosing recommendations vary by manufacturer, but should be titrated to reach target trough IgG values. Doses up to 400-600mg/kg may be needed after titration from lower doses.
C) In the treatment of CLL with hypogammaglobulinemia and frequent infections doses of 400mg/kg administered every 3-4 weeks has been used.
D) In post-transfusion purpura IVIG has been used with dosing similar to ITP.
E) In patients with or at risk of renal impairment the concentration and infusion rate should be minimized.
F) FDA pregnancy risk category C.

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IV. TOXICITY

Most adverse reactions associated with immune globulin IV (IGIV) are mild and transient and include flushing, hypertension or hypotension, malaise, back pain, myalgia, headache, nausea/vomiting, low-grade fever, chills, pruritus, urticaria, and rash (unspecified). Slowing or stopping the infusion usually allows these symptoms to resolve. Pretreatment with oral antihistamines and analgesics may help to alleviate these symptoms. The most frequent adverse reactions include:

A) Headache/aseptic meningitis.
B) Cough.
C) Fever.
D) GI symptoms.
E) Abdominal pain.
F) Arthralgias.

NOTE: Serious adverse events are rare but that have been reported with IVIG include: acute renal failure, hemolytic anemia, anaphylaxis, VTE, acute respiratory distress syndrome (ARDS), bronchospasm, seizures, tremor, Stevens-Johnson syndrome, epidermolysis, erythema multiforme, bullous rash (bullous dermatitis), pancytopenia, leukopenia, and hepatic dysfunction.

V. CLINICAL MONITORING

A) Serum IgG concentrations in hypogammaglobulinemia.
B) Platelet count in patients with ITP or post transfusion purpura.
C) BUN/Cr to monitor for renal impairment.
D) Clinically such as bleeding in ITP or frequency of infections in CVID.

NOTE: Risk factors for renal failure should be considered prior to administration. Sucrose free products may be preferred in those considered at risk.

VI. DRUG INTERACTIONS

Do not vaccinate patients with most live virus vaccines for at least 3 months after administration of IVIG. IVIG contains antibodies that can interact with certain live virus vaccines. IVIG should not be administered concomitantly with measles/mumps/rubella vaccines, MMR, rotavirus vaccine; or varicella virus vaccine live. Consult specific CDC guidelines for the most current clinical recommendations in accordance with the individual patient circumstances and the vaccine in question.