

Pediatric Hematology-Oncology
“Red Team”
Resident Handbook

Revised March 2011

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ANTIEMETICS

Pediatric Recommendations for Antiemetic Use with Chemotherapy

Approved by UCSF Pharmacy and Therapeutics Committee 5/14/2008; Revised 4/09

High Emetic Risk	Moderate Emetic Risk	Low Emetic Risk	Minimal Emetic Risk
Busulfan Cisplatin $\geq 50 \text{ mg/m}^2$ ♦ Cyclophosphamide $> 1500 \text{ mg/m}^2$ ♦ Carmustine (BCNU) $> 250 \text{ mg/m}^2$ Total Body Irradiation	Arsenic Trioxide Carboplatin ♦ Carmustine $\leq 250 \text{ mg/m}^2$ Cisplatin $< 50 \text{ mg/m}^2$ ♦ Cyclophosphamide $< 1500 \text{ mg/m}^2$ ♦ Cyclophosphamide (oral) Cytarabine $\geq 1 \text{ g/m}^2$ Cytarabine (intrathecal) Dactinomycin Daunorubicin Doxorubicin Epirubicin Etoposide (oral) Idarubicin Ifosfamide Imatinib Irinotecan Lomustine (CCNU) Melphalan $> 50 \text{ mg/m}^2$ Methotrexate $> 250 \text{ mg/m}^2$ Oxaliplatin $> 75 \text{ mg/m}^2$ Temozolomide (oral) Vinorelbine (oral) Radiation Therapy	Cytarabine $< 1 \text{ g/m}^2$ Docetaxel Doxorubicin (liposomal) Etoposide Fludarabine (oral) Gemcitabine Methotrexate $50\text{-}250 \text{ mg/m}^2$ Metaiodobenzylguanidine (MIBG) Methotrexate (intrathecal) Mitoxantrone Topotecan 5-Fluorouracil Vinblastine Vinorelbine	Alemtuzumab Asparaginase Bevacizumab Bleomycin Dasatinib Dexrazoxane Fludarabine Gemtuzumab ozogamicin Hydrocortisone (intrathecal) Hydroxyurea (oral) Melphalan (oral low-dose) Methotrexate $< 50 \text{ mg/m}^2$ Nelarabine Pentostatin Rituximab Thioguanine (oral) Vincristine

♦ Agents with prolonged emesis risk. Include oral antiemetics with discharge medications

FOR HIGH AND MODERATE EMETIC RISK CHEMOTHERAPY REGIMENS:

Patients ≥ 40 kg: See UCSF Adult Antiemetic Guidelines

Step 1:

- **dexamethasone** 10 mg/m²/dose (max 20 mg/dose) x 1, then 5 mg/m²/dose PO/IV q6h x 24 hrs
Note: (1) Requires Attending's approval
(2) Do not add dexamethasone if chemotherapy includes steroids or if patient is hyperglycemic or if prohibited by protocol (e.g., immunotherapy, brain tumors)
(3) If patient develops or has a history of hyperglycemia, glucosuria, or behavior changes, consider decreasing the dose to: dexamethasone 6 mg/m²/dose (max 6 mg/dose) x 1, then 3 mg/m² (max dose 3 mg) IV q6h x 24 hrs
- **Ondansetron** 0.15 mg/kg/dose PO/IV q8h (max 32 mg/day)

OR

aprepitant (Emend®):

Aprepitant may be considered in patients ≥ 40 kg AND ≥ 12 years receiving cisplatin for treatment of osteosarcoma.

Aprepitant should be given in combination with dexamethasone and ondansetron.

See Drug Interactions Table

- **aprepitant** 125 mg PO day 1, 80 mg PO daily days 2-3

OR

fosaprepitant dimeglumine 115 mg IV day 1, **aprepitant** 80 mg PO daily days 2-3

PLUS

- **dexamethasone** 10 mg/m² PO/IV day 1, 5 mg/m² PO/IV daily on days 2-4
- **ondansetron** 0.15 mg/kg/dose PO/IV day 1 (max 32 mg/day)

Step 2: Add any of the following

- **diphenhydramine** 0.5-1 mg/kg/dose IV/PO q6h as needed for nausea/vomiting (max dose = 50 mg)
- **scopolamine** 1.5 mg/patch
Notes: (1) Do not use in children < 3 years old
(2) 3-6 years = ½ patch q72h
(3) > 6 years = 1 patch q72h
(4) Scopolamine and diphenhydramine have additive anticholinergic effects
- **metoclopramide** 1 mg/kg/dose (max 40 mg/day) IV/PO q6h as needed + diphenhydramine 1 mg/kg/dose (max 50 mg/dose) IV/PO q6h
Note: (1) Must give with diphenhydramine to decrease risk of extrapyramidal reactions
(2) Continue diphenhydramine 24 hrs after last dose of metoclopramide
- **lorazepam** 0.05-0.1 mg/kg/dose (max 2 mg/dose) PO/IV q6 as needed

- **promethazine** 0.25-1 mg/kg/dose (max 25 mg/dose) PO/IV q6h as needed
Note: (1) Do not use in children < 5 years old. Increased risk for extrapyramidal symptoms, as well as for severe and potentially fatal respiratory depression.

Step 3: Add **dronabinol** (Marinol®) 2.5-5 mg PO q6h

Note: (1) ONLY for children > 10 years

LOW AND MINIMAL EMETIC RISK CHEMOTHERAPY REGIMENS:

Patients ≥ 40 kg: See UCSF Adult Antiemetic Guidelines

Step 1: Start before chemotherapy, and 4 hours after chemotherapy

- **ondansetron** 0.15 mg/kg/dose PO/IV (max 32 mg/day)

Step 2: Increase **ondansetron** 0.15 mg/kg/dose (max 32 mg/day) PO/IV q8h

Step 3: Add any of the following agents:

- **dexamethasone** 10 mg/m²/dose (max 20 mg/dose) x 1, then 5 mg/m²/dose IV q6h x 24h
Note: (1) Requires Attending's approval
(2) Do not add dexamethasone if chemotherapy includes steroids or if patient is hyperglycemic
(3) If patient develops or has a history of hyperglycemia, glucosuria, or behavior changes, consider decreasing the dose to dexamethasone 6 mg/m²/dose (max 6 mg/dose) x 1, then 3 mg/m² (max dose 3 mg) IV q6h x 24 hrs
- **diphenhydramine** 0.5-1 mg/kg/dose IV/PO q6h as needed for nausea/vomiting (max dose = 50 mg)
- **scopolamine** 1.5 mg/patch
Note: (1) Do not use in children < 3 years old
(2) 3-6 years = ½ patch q72h
(3) > 6 years = 1 patch q72h
(4) Scopolamine and diphenhydramine have additive anticholinergic effects
- **metoclopramide** 1-2 mg/kg/dose (max 40 mg/day) IV/PO q6h as needed + diphenhydramine 1 mg/kg/dose (max 50 mg/dose) IV/PO q6h
Note: (1) Must give with diphenhydramine to decrease risk of extrapyramidal reactions
(2) Continue diphenhydramine 24 hrs after last dose of metoclopramide.
- **lorazepam** 0.05-0.1 mg/kg/dose (max 2 mg/dose) PO/IV q6 as needed
- **promethazine** 0.25-1 mg/kg/dose (max 25 mg/dose) PO/IV q6h as needed
Note: (1) Do not use in children < 5 years old. Increased risk for extrapyramidal symptoms, severe and potentially fatal respiratory depression

Step 4: Add **dronabinol** (Marinol®) 2.5-5 mg PO q6h

Note: (1) ONLY for children > 10 years

ANTIEMETIC ORAL DOSAGE FORMULATIONS

	Tablet/Capsule Strengths	Liquid
Aprepitant (Emend [®])	40, 80, 125 mg	---
Dexamethasone (Decadron [®])	0.5, 0.75, 1, 1.5, 2, 4, 6 mg	1 mg/ml
Diphenhydramine (Benadryl [®])	25, 50 mg	12.5 mg/5 ml
Dronabinol (Marinol [®])	2.5, 5, 10 mg	---
Granisetron (Kytril [®])	1 mg	2 mg/10 ml
Haloperidol (Haldol [®])	0.5, 1, 2, 5, 10, 20 mg	2 mg/ml
Lorazepam (Ativan [®])	0.5, 1, 2 mg	2 mg/ml
Metoclopramide (Reglan [®])	5, 10 mg	5 mg/5 ml
Olanzapine (Zyprexa [®])	2.5, 5, 7.5, 10 mg	--
Ondansetron (Zofran [®])	4, 8 mg	4 mg/5 ml
Prochlorperazine (Compazine [®])	5, 10 mg	--
Promethazine (Phenergan [®])	12.5, 25 mg	6.25 mg/5 ml

APREPITANT DRUG INTERACTIONS

Aprepitant can increase plasma concentrations of drugs that are metabolized through the CYP3A4 pathway.

- Chemotherapy agents metabolized by CYP3A4 pathway include etoposide, docetaxel, paclitaxel, irinotecan, ifosfamide, imatinib, vinorelbine, vinblastine, and vincristine
- *Docetaxel*: Studies using aprepitant have shown no clinically significant change in docetaxel pharmacokinetics
- *Vinorelbine*: Studies using aprepitant have shown no clinically significant change in docetaxel pharmacokinetics
- *Cyclophosphamide and Ifosfamide*: Drug activation and metabolism dependent on CYP3A4. Aprepitant has the potential to decrease drug activation, as well as increase drug level concentrations.
 - There has been 1 published case report of aprepitant and ifosfamide-induced encephalopathy.
 - Limited pharmacokinetic data is available regarding use of aprepitant during cyclophosphamide and ifosfamide chemotherapy

Aprepitant can decrease plasma concentrations of drugs that are metabolized through the CYP2C9 pathway

- Coadministration of aprepitant with warfarin may result in a decrease in PT/INR. Close monitoring during 7-10 days following a 3 day regimen of aprepitant is recommended.
- Aprepitant can decrease efficacy of oral contraceptives

Aprepitant is metabolized through the CYP3A4 pathway

- Drugs that inhibit CYP3A4 (ex. voriconazole, fluconazole, ritonavir, clarithromycin) may increase plasma concentration of aprepitant
- Drugs that induce CYP3A4 (ex. carbamazepine, phenytoin, rifampin) may decrease plasma concentrations of aprepitant

REFERENCES:

1. Smith AR, Repka TL, Weigel BJ. Brief Report: Aprepitant for the Control of Chemotherapy Induced Nausea and Vomiting in Adolescents. *Pediatr Blood Cancer* 2005; 45: 857-560.
2. Hesketh PJ, Grunberg SM, Gralla RJ et al. The Oral Neurokinin-1 Antagonist Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting: A Multinational, Randomized, Double-Blind, Placebo-Controlled Trial in Patients Receiving High-Dose Cisplatin- The Aprepitant Protocol 052 Study Group. *Journal of Clinical Oncology*, Vol 21, No 22, 2003.
3. Massaro AM, Lenz KL. Aprepitant: A Novel Antiemetic for Chemotherapy-Induced Nausea and Vomiting. *The Annals of Pharmacotherapy*, 2005 January, Volume 39.
4. Aprepitant (Emend[®]) Package Insert, November 2007
5. Fosaprepitant (Emend[®]) for Injection) Package Insert, January 2008
6. National Comprehensive Cancer Network. 2008 Antiemetic Guidelines
7. Kris MG, Hesketh PJ, Somerfield MR et al. American Society of Clinical Oncology Guideline for Antiemetics in Oncology: Update 2006. *J Clin Oncol*, June 2006; 24:2932-2947.
8. Roila F, Feyer P, Maranzano E. Antiemetics in Children Receiving Chemotherapy. *Support Care Cancer* (2005) 13: 129-131.
9. Nygren P, Hande K, Petty K. Lack of Effect of Aprepitant on the Pharmacokinetics of Docetaxel in Cancer Patients. *Cancer Chemother Pharmacol* (2005) 55: 609-616.
10. Loos WJ, de Wit R, Freedman SJ. Aprepitant when Added to a Standard Antiemetic Regimen Consisting of Ondansetron and Dexamethasone Does not Affect Vinorelbine Pharmacokinetics in Cancer Patients. *Cancer Chemother Pharmacol* (2007) 59: 407-412.
11. Lasseter KC et al. Tolerability of Fosaprepitant and Bioequivalency to Aprepitant in Healthy Subjects. *Journal of Clinical Pharmacology*, 2007; 47: 834-840.

TRANSFUSION GUIDELINES

- All Pediatric Oncology patients should get **irradiated blood products**. If patient is CMV-antibody negative, patients should also get **CMV-negative blood products**.
 - Irradiation of blood components: transfusion associated-GVHD may occur when immunologically competent leukocytes are transfused into an immunocompromised recipient. Leukocyte reduction is not a substitute for irradiation.
 - All patients should receive **leukoreduced** blood products. All blood products at UCSF are **leukoreduced**. There is no need to use a leukopoor filter with leukoreduced blood products (an older convention when blood was collected, then leukoreduced at bedside, which was much less efficient. All blood is leukoreduced in the Blood Bank now at time of collection). Leukoreduction reduces transmission of CMV (because the virus resides intracellularly in white blood cells), reduces alloimmunization to HLA antigens, and reduces the incidence of febrile transfusion reactions.

1) PRBC

- a) **Indications:** Transfuse if Hb < 7 or if symptoms of anemia such as dizziness, fatigue, or headache. For patients with aplastic anemia (AA), transfusion guidelines are much more conservative → transfuse if Hb < 6 or symptoms.
- b) **Pre-medication** with Tylenol and/or Benadryl is not necessary unless the patient has a history of previous reactions. (See Reactions sections below).
- c) **Dose:** Usual volume is 10-15 mL/kg over 3-4 hours. If Hb < 5 and anemia is chronic, transfusion volume should be 5 mL/kg over 4 hours & repeated prn after clinical assessment.
*** 10-15 mL of PRBC/kg will raise the hematocrit by 10-15% or raise the Hb concentration by 2-3 g/dL.**

2) PLATELETS

- a) **Indications:**
 - i) Prophylactic transfusions: platelet count <10,000 or <15,000 if febrile, since platelets have decreased function in presence of fever. Platelet transfusions are of little value in patients with immune thrombocytopenia, since the transfused platelets will be destroyed rapidly.
 - ii) Keep above 30,000 for LPs **OR** IM injections **OR** in patients with mucositis
 - iii) Keep above 30,000 in patients with brain tumors during radiation therapy and in early phase of chemotherapy.
 - iv) Keep above 50,000 (most surgeons prefer >75,000) before central line placement **OR** with bleeding
 - v) There is no need for platelet transfusions prior to bone marrow aspirates/biopsies.
- b) **Pre-medication for platelet transfusions** (See Reactions sections below).
- c) **Dose:** One platelet unit (prepared by centrifugation of whole blood after its collection) is about 50 mL of platelets and plasma. (This product is not available at UCSF). One adult platelet pheresis unit (obtained by automated apheresis equipment) is comparable to a pool of ~6 random donor platelet units. Volume is about 250 mL. A pedi-pheresis is 1/2 an adult platelet pheresis unit (~3 platelet units). Transfuse platelets over 30-60 minutes (depending on total volume and size of patient); faster rates of infusion may result in platelet shearing.

- i) Guidelines: 5 to 10 mL/kg of either a platelet or pheresis platelet unit should result in a 50,000-100,000 increase in platelet count. For children over 10 kg, a dose of 1 platelet unit per 10 kg should produce the same results. A post-transfusion platelet count (if indicated) may be drawn as early as 10 minutes after transfusion.
- ii) Pheresis platelet units limit donor exposures and infection risk.
- iii) Platelets can be concentrated (i.e., volume-reduced) for very fluid-sensitive patients, but this is rarely indicated and results in up to 50% platelet loss.

3) FRESH FROZEN PLASMA (FFP)

- a) Contains all the clotting factors in plasma (but not concentrated).
- b) **Indications:** PT or PTT >1.5 times normal or bleeding with abnormal PT/PTT and platelet count >50,000.
- c) **Dose:** 10-15 mL/kg q8-12 hours (will raise individual clotting factors by 15-20%) transfused over 2-4 hours.

4) CRYOPRECIPITATE

- a) Contains fibrinogen in higher concentration than FFP. as well as factor VIII, von Willebrand factor, and factor XIII. Concentration of these four clotting factors is 5-6 times more than in FFP.
- b) **Indications:**
 - i) Hypofibrinogenemia <75 **OR** <100 and bleeding.
 - ii) Factor XIII deficiency and bleeding.
- c) **Dose:** A dose of 1 to 2 units/10 kg body weight will raise fibrinogen level by 60-100 mg/dL and may be transfused as quickly as possible (each unit is ~15-20 mL). In infants, one bag is sufficient to achieve hemostasis.

TRANSFUSION REACTIONS

- 1) **FEBRILE NON-HEMOLYTIC TRANSFUSION REACTIONS (FNHTR):** Likely due to cytokines generated by white blood cells during storage. Leukoreduction at collection may further prevent FNHTR. A fever (>1°C increase in temperature) often is accompanied by chills (generally no rigors) and overall discomfort.
 - a) **Management:**
 - i) Must rule-out fever from infected blood product.
 - (1) Stop transfusion and send bag/tubing promptly to blood bank for blood product culture
 - (2) Send blood cultures from patient (central line is fine, also peripheral if hypotensive/septic-appearing)
 - ii) We recommend prophylactic pre-medication with antipyretic after 1 reaction.
 - (1) Pre-medicate with acetaminophen (10-15 mg/kg PO) 30 to 60 minutes before subsequent transfusions.
- 2) **ALLERGIC REACTIONS:** are caused by an antibody response in recipients to soluble plasma proteins within the blood product. Allergic reactions are not prevented by WBC reduction. The severity of the allergic reaction can range from mild localized urticaria, pruritus, and flushing to bronchospasm and anaphylaxis. Fever is usually absent.

a) **Management:**

- i) Mild Allergic Reactions: Treat with Benadryl (1.0-1.5 mg/kg PO/IV; max 50 mg) +/- hydrocortisone (1 mg/kg IV); if the rash decreases and the patient feels well and shows no sign of fever, chills or vasomotor instability, may proceed with the transfusion.
- ii) Pre-medicate with Benadryl +/- hydrocortisone 1 hour before transfusion for prevention of recurrent hives.
- iii) Moderate or Recurrent Allergic Reactions: Benadryl (1 mg/kg PO/IV) 1 hour before transfusion AND a corticosteroid (e.g., hydrocortisone 1 mg/kg IV) 2 to 6 hours before transfusion. Washed components should be used in cases of extreme reactions, but be aware that washing results in up to 50% cell loss (more for platelets than for PRBCs).

3) **ANAPHYLACTIC REACTIONS**: due most often to anti-IgA antibodies in IgA-deficient patients. Variety of symptoms including nausea, vomiting, shock and bronchospasm.

a) **Management:**

- i) Stabilize with Benadryl (1.0-1.25 mg/kg PO/IV; max 50 mg), hydrocortisone (1 mg/kg IV) and Epinephrine (0.01 mg/kg IV/SC; max dose 0.5 mg. Usually given as 0.01 cc/kg SC of 1:1,000 solution or 0.1 cc/kg IV of 1:10,000 solution).
- ii) Must get washed blood products AND pre-medicate as described above for moderate or recurrent allergic reactions.
- iii) Document IgA deficiency in pre-transfusion clot in Blood Bank.

4) **ALLOIMMUNIZATION AND PLATELET REFRACTORINESS**

- a) Definition of platelet refractoriness: corrected count increment (CCI) of <7500 1 hour post-transfusion on 2 consecutive transfusions. Platelet refractoriness can be secondary to development of anti-HLA and/or anti-platelet antibodies (immune-mediated) or non-immune causes such as splenomegaly, fever, sepsis, bleeding, and antibiotic therapy.
- i) $CCI = (\text{platelet increment}) \times (\text{bsa}) / (\text{number of platelets transfused})$
 - ii) Immune-mediated refractoriness has minimal increment at 1 hour and 24 hours post-transfusion, non-mediated refractoriness traditionally has an adequate initial increment at 1 hour but poor platelet increment at 24 hours post-transfusion.

b) **Management:**

- i) Make sure patient is platelet refractory with an immune-mediated etiology.
 - (1) Treat infection if present
 - (2) Obtain 10-60 minute post-transfusion platelet count x 2 (see CCI above). Blood Bank will calculate CCI for you. If CCI <7500, patient is refractory to platelets.
 - (3) Patients who have immune refractoriness after ABO-identical platelets should be screened for the presence of HLA antibodies.
- ii) For platelet refractoriness, recommend using crossmatched platelets first.
- iii) Recommend HLA-matched platelets for severely alloimmunized patients.

5) **ACUTE HEMOLYTIC REACTIONS**

- a) Usually due to ABO-incompatibility
- b) Can occur within minutes of transfusion to several hours after transfusion.
- c) Signs and symptoms: fever, chills, low back pain, hypotension, vomiting, diarrhea, oliguria and renal failure, unexplained bleeding, death.
- d) Thought to be due mostly to IgM binding and complement activation.

- e) Lab findings: hemoglobinemia and/or hemoglobinuria (red urine with no RBCs on urinalysis), anemia, and positive direct antiglobin test (direct Coombs).
- f) **Management:**
 - i) Stop transfusion. Send blood to blood bank for analysis.
 - ii) Give normal saline (10 cc/kg IV).
 - iii) **If necessary:** Epinephrine (0.01 mg/kg IV/SC; max dose 0.5 mg. Usually given as 0.01 cc/kg SC of 1:1,000 solution or 0.1 cc/kg IV of 1:10,000 solution) and Hydrocortisone (1 mg/kg IV).
 - iv) Maintain good urine output (>1 mL/kg) with one and a half (1 1/2) maintenance IVF. Lasix may be needed.

6) DELAYED HEMOLYTIC REACTIONS

- a) Occurs from 1-7 days after a transfusion secondary to minor incompatibilities such as Rh, Kell, Fy^a or Jk^a.
- b) Represents an anamnestic response in someone who has previously been immunized to red cell antigens. Occurs in a patient in whom no red cell antibody was detected at the time of compatibility testing.
- c) May be symptomatic or asymptomatic
- d) Signs and symptoms: Most common is decrease in hemoglobin. Less commonly can see abdominal pain, jaundice, and fever.
- e) Lab findings: anemia, elevated bilirubin, reduced haptoglobin and positive direct antiglobulin test (direct Coombs).
- f) **Management:**
 - i) IV fluids to maintain good urine output
 - ii) Transfuse with appropriately cross-matched blood.

- 7) **TRANSFUSION-RELATED ACUTE LUNG INJURY (TRALI):** is an uncommon (estimated at 1/5,000 transfused units) yet potentially fatal transfusion reaction that recently has become the leading cause of death from transfusion in the United States. It typically occurs during or within 6 hours of transfusion and presents with respiratory distress (tachypnea/dyspnea) resulting from noncardiogenic pulmonary edema (normal central venous pressure and pulmonary capillary wedge pressure), hypotension, fever, and severe hypoxemia. Transient leucopenia can be observed within a few hours of the reaction.
- a) Exact mechanism remains uncertain, two hypotheses are proposed:
 - i) Antibody-mediated hypothesis: anti-granulocyte or anti-HLA I or II antibodies (from donor or recipient) attach to corresponding antigen on neutrophils causing sequestration and activation of neutrophils within the lungs
 - ii) Neutrophil priming hypothesis: two-hit mechanism, the first event is the clinical situation within the recipient (i.e., surgery, infection, or trauma) which primes neutrophils, and the second event is transfusion of "bioactive factors" such as cytokines, IL-6, IL-8, bioactive lipids, or anti-HLA/anti-granulocyte antibodies which produces neutrophil sequestration within the lungs.
 - b) Associated with all blood product transfusions; however, plasma products account for majority of TRALI fatalities.
 - c) **Management:** Supportive care for signs and symptoms of respiratory distress. In severe cases, intubation may be necessary. Avoid diuretics as this may worsen symptoms. The role of steroids is not clear. CXR will demonstrate bilateral pulmonary infiltrates. TRALI usually improves 24 to 48 hours from onset of symptoms.

- i) Stop transfusion
- ii) Send blood bags to Blood Bank
- iii) Notify Blood Bank of possible TRALI reaction
- iv) If further transfusion is indicated, may transfuse but donor(s) implicated in the transfusion reaction should be avoided until further investigation by the Blood Bank.

PHERESIS AND EXCHANGE TRANSFUSION

Definition and Types of Pheresis

Apheresis means selectively collecting a blood component from blood. Cytopheresis selectively removes cellular blood components: leukopheresis moves white blood cells; platelet apheresis collects platelets; and erythrocytopheresis collects or exchanges red blood cells. Plasmapheresis selectively removes the non-cellular portion of blood, specifically plasma.

Apheresis may also be initiated to replace a missing element in a patient who, for hemodynamic reasons, cannot tolerate a simple transfusion, e.g., a red cell transfusion in an anemic patient with severe congestive heart failure.

Methods of pheresis

- Manual apheresis
- Automated apheresis
 - Centrifugation (continuous) – available at UCSF
 - Immunoabsorption column – *Staphylococcus* protein A (ProSORBA A) binds IgG – no longer available
 - Membrane – not available at UCSF

Possible indications for pheresis

Refer to Journal of Clinical Apheresis 22:106-175 (2007) or www.apheresis.org for a complete and updated list of indications.

- Autoimmune Disease (e.g., acute Guillain Barré syndrome, myasthenia gravis, Goodpasture syndrome)
- Coagulopathy/hepatorenal syndrome
- Hyperviscosity
- Hyperacute solid organ rejection
- Hematologic: HUS; TTP; ALL or AML with hyperleukocytosis or symptoms of leukostasis (e.g., CNS or pulmonary symptoms)

<u>Indication</u>	<u>Replacement Fluid</u>
Autoimmune disease	5% albumin
Coagulopathy	FFP
Hyperviscosity	5% albumin
Cryoglobulinemia	Warm 5% albumin
Cold agglutinin hemolysis	Warm 5% albumin
WBC reduction	5% albumin plus/minus FFP
HUS	FFP and liquid plasma (lower factors 5 and 8)

Stem Cell Collection

No replacement needed

Relationship of Plasma Exchange Volume and Removal of Intravascular Substance

Plasma volume = 40 mL/kg

(Note: Table below is for 70 kg adults, but can be adjusted for children)

<u>Plasma Volume Removed</u>	<u>Volume (mL)</u>	<u>Fraction Remaining (%)</u>
0.5	1400	60
1.0	2800	38
1.5 (routine at UCSF)	4200	22
2	5600	15

Frequency of Exchange: usually qday x 2, then qoday x 5-6 days. Little benefit with <2x/week, as factor reaccumulates.

Pearls for Therapeutic Apheresis

<u>Item</u>	<u>Pheresis removes</u>	<u>Replace</u>
Volume	60-80 mL/kg	+/- 15% of volume removed
Osmolarity	Plasma proteins	5% albumin or FFP
Na	135-145 mEq/L	ACDA (510 mEq/L) LR (510 mEq/L) NS (154 mEq/L) or albumin (145 mEq/L);
K	3.5-5 mEq/L	4 mEq/L albumin
Ca	8.5-10.5 mg/dL	10 mg/dL albumin
Mg	1.6-2.7 mg/dL	5 mg/dL albumin
Hemostasis factors citrate	Fibrinogen, factors, liquid plasma + CaCl	FFP + 1 mL 10% CaCl;

- Machine must be primed due to 70 mL deadspace (current machine). If patient is less than 15 kg, prime with PRBCs.
- Start with a hematocrit >25 if possible, as helps with interface for pheresis
- Platelet count does not matter unless stem cell collection in which case you want a platelet count of 50,000 (can do less and transfuse post-collection)
- Check lytes (especially ionized calcium) and fibrinogen before procedure; if fibrinogen is low, use FFP as replacement fluid
- Rely on the very helpful 11th floor pheresis unit nurses (353.1538; will have pager for on-call nurse if after-hours). They can walk you through the orders and also have a very helpful book that specifies the details.

Complications

- Related to procedure:
 - Chills
 - Citrate toxicity (hypocalcemia, hypokalemia, nausea/vomiting)
 - Hypotension
 - Hypersensitivity to FFP
 - Infection from blood products (e.g. hepatitis)

- Change in drug concentrations – especially if small volume of distribution or high protein binding (often give increased dose on pheresis day; don't give antibiotics immediately prior to pheresis)
- Volume overload
- Access (a large bore line is necessary; usually Groshong catheter is placed by Pediatric Cardiology fellow – confirm minimum size with pheresis nurses prn)
- Depletion of plasma constituents: fibrinogen, C3, immunoglobulins, potential increased risk of bleeding (dilutional thrombocytopenia/coagulopathy) or thrombosis). Increased risk of infection has not been documented in literature.

EXCHANGE TRANSFUSION

Purpose

In an exchange transfusion, the patient's red cells are removed and replaced by normal red cells. The exchange prevents the removed sickle cells from participating in new vaso-occlusive events, reduces hemolytic complications, and provides added oxygen carrying capacity, while decreasing the blood viscosity.

Indications for Exchange Transfusion

Used in situations where the amounts of blood needed to either reduce the % HbS or provide oxygen carrying capacity will cause the hemoglobin to exceed 10 g/dL

- Stroke. Start exchange transfusion immediately after diagnosis of infarct (not hemorrhagic stroke) via non-contrast CT. Additional studies, such as MRI/MRA, should await the completion of the red cell exchange. Goal: hemoglobin S <30% and hemoglobin close to, but not greater than, 10 g/dL.
- Severe acute chest syndrome. Indications for exchange transfusion include cases in which hypoxia not controllable with oxygen therapy; patients requiring ventilator therapy, multilobar process; and lack of clinical improvement after a simple red cell transfusion. Goal: hemoglobin S <30% and hemoglobin close to, but not greater, than 10.
- Priapism
- Organ failure

Protocol

Early discussions with the blood bank resident and attending will be informative and will facilitate the process.

1. Calculate exchange volume as 1.5 red cell volumes.
2. Red cell volume = hematocrit × total blood volume. (Assume total blood volume is 70 cc/kg if over 20 kg, 85 mL/kg if under 20 kg)
3. Perform manual exchange as follows:
 - a. Bleed 5-10 mL /kg, then infuse same amount saline
 - b. Bleed 5-10 mL/kg, then infuse packed red cells (sickle dex negative and phenotypically matched for C, E, and Kell) (amount = 1 to 1.25 fold the amount of blood removed in bleeds)
 - c. Repeat steps 3a and 3b until volume of packed cells administered is equal to planned exchange volume (up to three or even four repeats for large adults)

4. Automated red blood cell exchange may also be arranged with the Apheresis Hemodialysis Unit (usual protocol).

Pearls

- Hb > 10 g/dL will lead to viscosity-related complications in sickle cell disease (caution in patients with relatively high baseline Hb – i.e., SC disease)
- Use opposite arms for draw and return

FEVER +/- NEUTROPENIA: GUIDELINES FOR MANAGEMENT

All fevers in pediatric oncology patients are considered **oncologic emergencies**. Our patients require immediate assessment, as untreated sepsis with neutropenia can lead quickly to clinical decompensation including hypotension and death. Drawing of CBC with differential and appropriate cultures and administration of antibiotics must be performed within **one hour** of patient arrival to ED. **DO NOT WAIT FOR LAB RESULTS TO RETURN BEFORE ADMINISTERING ANTIBIOTICS**. Our patients also must not wait in the waiting room with other ill patients. Febrile neutropenic and otherwise clinically concerning patients will be admitted to UCSF/7 Long **ONLY** after appropriate Emergency Room evaluation and stabilization. Discuss all patients with on-call pediatric hematology-oncology fellow: 415.476.3831 (24 hour answering service).

FEVER: any oral or axillary temperature ≥ 38.3 °C (101.0 °F) OR a temperature 38.0 - 38.2 °C (100.4 - 100.9 °F) sustained for one hour

NEUTROPENIA: absolute neutrophil count (ANC) < 500

INITIAL ASSESSMENT

- Vital signs: temperature (oral or axillary; not rectal), blood pressure, heart rate, respiratory rate, oxygen saturation
- History: recent viral illnesses or otitis media, other localizing signs/symptoms, ill contacts, most recent chemotherapy administration, current medications, and prior infections (line infections or bacteremia/sepsis, pneumonia, UTIs, viral illnesses [including varicella], fungal disease, etc.)
- Physical exam: Complete physical examination with particular visual attention to central line site, mouth/teeth, and perianal area
- Laboratory studies: STAT CBC with differential, aerobic and anaerobic blood cultures from central line, peripheral blood cultures if septic-appearing or has central line erythema, urinalysis & urine culture (if able to obtain clean catch specimen; check with Pediatric Oncology fellow before attempting catheterization), DFA for respiratory viruses when indicated, etc.
- Radiology studies: PA & lateral CXR if clinically indicated; abdominal plain films, ultrasound, or CT if concerning exam
- Administer appropriate antibiotics promptly via central line (i.e., do not wait for CBC results to return, urine culture to be obtained if difficult acquisition, or for radiology study to occur; administer immediately after CBC and blood cultures drawn)! **Prompt administration of antibiotics are life-saving**. If patient is/becomes hypotensive or experiences rigors after antibiotic administration, be concerned for gram-negative sepsis and immediately discontinue use of central line, instead continuing to resuscitate with fluids and antibiotics via a peripherally-placed i.v.
- Patients may have acetaminophen (Tylenol) for fever reduction after discussing with Pediatric Oncology fellow or attending; please do not ever administer aspirin or any form of NSAIDs (e.g., ibuprofen, Advil, Motrin, naproxen, ketorolac, etc.) due to platelet inactivation effects in the setting of chemotherapy-associated thrombocytopenia.

ADMISSION CRITERIA

All patients with fever and neutropenia (as defined above) require hospital admission following appropriate initial assessment. Choice of i.v. antibiotics depends upon their “high risk” vs. “low risk” classification and other clinical factors. Febrile non-neutropenic patients who are clinically well-appearing and considered “low risk” may receive broad-spectrum i.v. antibiotics after a blood culture has been obtained and be discharged with close outpatient follow-up.

FEVER AND NEUTROPENIA (ANC < 500)

HIGH RISK (any criterion below qualifies patient as high-risk)

- Clinically unstable and/or with abnormal blood pressure or pulses, chills, or rigors
- Children with hematologic malignancies (leukemia or lymphoma) in induction, consolidation, or delayed intensification phases of chemotherapy
- Children with hematologic malignancies (leukemia or lymphoma) with active or relapsed disease
- Neutropenia anticipated to persist longer than 7 days
- Children with metastatic solid tumors with active bone marrow involvement
- Any inpatient hospitalized for >3 days who develops a new fever
- Any patient who has received a stem cell transplant and who has a double lumen Broviac in place
- Serious infection (e.g., pneumonia, cellulitis, significant mucositis, typhlitis/acute abdomen, perirectal abscess)

LOW RISK (must meet all criteria below & have no high-risk features)

- Neutropenia anticipated to resolve within 7 days
- Normal blood pressure, perfusion, respiratory rate, and oxygen saturation and looks clinically well
- Normal mental status
- No focus of serious infection (e.g., pneumonia, cellulitis, significant mucositis, typhlitis/acute abdomen, perirectal abscess)

FEVER WITHOUT NEUTROPENIA (ANC > 500)

Clinically stable

- **No central line:** obtain CBC with differential & peripheral blood cultures and perform physical exam; no antibiotics necessary if well-appearing and no focal source of infection; repeat q24h for recurrent fever (up to three days). Obtain CXR and/or send DFA if clinically indicated.
- **Central line (Broviac or Port-a-Cath):** obtain CBC with differential and blood cultures from central line & perform physical exam; administer ceftriaxone 50 mg/kg i.v. q24h for up to three days if remains febrile. Obtain CXR and/or send DFA if clinically indicated. If inpatient and stable with non-neutropenic fever, may obtain CBC & blood cultures and observe closely without antibiotics (please discuss this management with Pediatric Oncology fellow or attending).

Clinically unstable: follow high risk fever & neutropenia guidelines.

ANTIBIOTIC RECOMMENDATIONS

CLINICAL SETTING	FIRST CHOICE OF ANTIBIOTICS*	ANTIBIOTICS FOR PENICILLIN-ALLERGIC PATIENTS
SEPTIC SHOCK WITH NEUTROPENIA (I.E., PICU ADMISSION)	Meropenem 20 mg/kg q8h AND **Tobramycin 2.5 mg/kg q8h AND Vancomycin 15 mg/kg q6h	same
HIGH RISK NEUTROPENIA & CLINICALLY UNSTABLE	Piperacillin/tazobactam (Zosyn) 80 mg/kg q8h AND **Tobramycin 2.5 mg/kg q8h AND Vancomycin 15 mg/kg q6h	Ciprofloxacin 15 mg/kg q12h AND Tobramycin 2.5 mg/kg q8h AND Vancomycin 15 mg/kg q6h
HIGH RISK NEUTROPENIA & CLINICALLY STABLE	Piperacillin/tazobactam (Zosyn) 80 mg/kg q8h AND **Tobramycin 2.5 mg/kg q8h ***(Vancomycin for some patients)	Ciprofloxacin 15 mg/kg q12h AND Tobramycin 2.5 mg/kg q8h
LOW RISK NEUTROPENIA & WITHOUT SOURCE	Ceftazidime 50 mg/kg q8h	Aztreonam 40 mg/kg q8h OR Ciprofloxacin 15 mg/kg q12h
LOW RISK NON-NEUTROPENIA	Ceftriaxone 50 mg/kg q24h	Ciprofloxacin 15 mg/kg q12h

* If there is an obvious clinical source of fever, treat for fever & neutropenia per above classification and add other antibiotics as necessary (e.g., add **vancomycin** initially for any central line erythema/discharge or skin breakdown, regardless of high or low risk status).

** For patients with renal dysfunction/failure or those who have recently received highly nephrotoxic chemotherapy (e.g., osteosarcoma patient s/p high dose methotrexate, brain tumor or osteosarcoma patient s/p cisplatin), use **ciprofloxacin** instead of tobramycin for double coverage. Give maintenance i.v. hydration and follow daily creatinine levels. If using concomitant vancomycin, follow drug levels frequently. Recall that Ambisome is also highly nephrotoxic (consider voriconazole in the setting of renal insufficiency for alternative anti-fungal coverage if appropriate).

*** Patients with history of ara-C chemotherapy administration (particularly intermediate- and high-dose, as in high risk & relapsed ALL and AML patients) have markedly higher incidence of viridans group *Streptococcus* infections and should also always receive **vancomycin** in context of febrile neutropenia.

MANAGEMENT OF HOSPITALIZED FEBRILE AND NEUTROPENIC PATIENTS

Obtain blood cultures q24h from central line while patient is febrile. Send subsequent peripheral blood cultures, urine cultures, DFAs, etc. as clinically indicated. Initial broad-spectrum i.v. antibiotic choice is guided by the recommendations above. Modification of initial regimen should occur in the following clinical situations:

- “Narrowing” of i.v. antibiotic coverage for positive blood cultures based upon resultant organism(s) and susceptibilities. *Caveat*: maintain at least ceftazidime-level of broad spectrum coverage in a neutropenic patient (e.g., do not narrow to cefazolin for pan-sensitive *E. coli* line infection or UTI if ANC < 500).
- Broad-spectrum i.v. antibiotics should be continued until patient defervesces AND is no longer neutropenic, but regimen may be switched to monotherapy in certain clinical situations (see below).
- Central catheters should be removed for:
 - persistently positive blood cultures while on appropriate antimicrobials (>48 hours)

- line tunnel infection
- any fungemia
- *Bacillus* infections
- *Persistent hypotension despite antibiotics*

Consider catheter removal in patients with multiple line infections or bacteremia with same organism(s), as catheter may be persistently colonized and unable to be cleared with antimicrobials.

Management of fever in hospitalized high risk febrile neutropenic patients

- Continue piperacillin/tazobactam (Zosyn) and tobramycin as above. If culture-negative, afebrile ≥ 48 hours, AND well-appearing, but still neutropenic, may discontinue tobramycin at ~48-72 hours. Continue Zosyn until ANC > 500 (or absolute monocyte count (AMC) > 100 and rising neutrophil count, depending on clinical situation and primary oncology team's recommendation).
- Add vancomycin for any central line erythema, skin breakdown, significant oral mucositis, and preliminary blood culture positivity for gram(+) cocci. Check vancomycin trough before third dose. **Always obtain peripheral blood culture before vancomycin initiation!**
- If persistent fever x 72 hours, consider empiric addition of i.v. anti-fungal agent (e.g., liposomal amphotericin or voriconazole), particularly in patients with leukemia or lymphoma. Monitor renal function closely and hydrate appropriately. Consider imaging studies (sinus, neck, chest, abdomen, and/or pelvis CT) to assess for fungal disease (and, rarely, occult abscess); imaging may be deferred until ANC rising.
- New fever occurrence in previously afebrile hospitalized high risk neutropenic patient (who remains on piperacillin/tazobactam due to neutropenia) should prompt re-addition of tobramycin and initiation of empiric anti-fungal therapy. Consider imaging studies.

Management of fever in hospitalized low risk febrile neutropenic patients

- Continue ceftazidime until ANC > 500 (or AMC > 100 and rising ANC, depending on clinical situation and primary oncology team's recommendation), even when afebrile and culture-negative.
- Add vancomycin for any central line erythema, skin breakdown, and preliminary blood culture positivity for gram(+) cocci. Check trough before third dose.
- If persistent fever x 72 hours, consider discontinuation of ceftazidime and initiation of piperacillin/tazobactam (Zosyn) and tobramycin.
- If persistent fever x 5 days, add i.v. anti-fungal agent (e.g., liposomal amphotericin or voriconazole). Monitor renal function closely and hydrate appropriately, especially when receiving other nephrotoxic therapies. Consider imaging studies (sinus, neck, chest, abdomen, and/or pelvis CT) to assess for occult abscess and fungal disease; imaging may be deferred until ANC rising.
- New fever occurrence in previously afebrile hospitalized low risk neutropenic patient should prompt discontinuation of ceftazidime, initiation of piperacillin/tazobactam and tobramycin, and consideration of empiric anti-fungal therapy. Consider imaging studies.

UCSF CHILDREN'S HOSPITAL

PEDIATRIC ANTIMICROBIAL DOSING GUIDELINE FOR CHILDREN > 1 MONTH OF AGE

Approved by the Antibiotic Advisory Subcommittee and the Pharmacy and Therapeutics Committee (November 1998) and revised (May 2009); relevant selections included for Pediatric Hematology-Oncology

http://clinicalpharmacy.ucsf.edu/idmp/peds_home.htm

ANTIBIOTICS	Creatinine clearance ≥50 mL/min/1.73m ² OR renal function ≥ 50% of normal	Creatinine clearance 10-50 mL/min/1.73m ² OR renal function = 10-50% of normal	Creatinine clearance ≤10 mL/min/1.73m ² OR renal function ≤10% of normal	MAXIMUM DAILY DOSE
Aztreonam	<i>Febrile neutropenia (if penicillin-allergic):</i> 40 mg/kg q8h	20 mg/kg q8h	13.3 mg/kg q8h	2 g q8h
Cefepime	<i>Febrile neutropenia:</i> 50 mg/kg q8h	>30% of normal clearance 50 mg/kg q12h 10-30% of normal clearance 50 mg/kg/dose q24h	25 mg/kg q24h	2 g q8h
Ceftazidime	50 mg/kg q8h	50 mg/kg q12h	50mg/kg q24-48h	2 g q8h
Ceftriaxone	50 mg/kg q24h <i>Meningitis:</i> 50 mg/kg/dose q12h	No change No change	No change No change	1 g q24h 2 g q12h
Ciprofloxacin IV	15 mg/kg q12h	10-30% of normal clearance 7.5 mg/kg q12h	7.5 mg/kg q12h	400 mg q12h
Clindamycin IV	10 mg/kg q8h	No change	No change	900 mg q8h
Imipenem	20 mg/kg q6h	10 mg/kg q6-8h	10 mg/kg q12h	1 g q6h
Meropenem Indicated for suspected meningitis or history of seizures	20 mg/kg q8h	25-50% of normal clearance 20 mg/kg q12h 10-25% of normal clearance 10 mg/kg q12h	10 mg/kg q24h	1 g q8h
Metronidazole IV/PO	10mg/kg q8h	No change	10 mg/kg q12h	500 mg q6h
Piperacillin/ Tazobactam (Zosyn®)	80 mg piperacillin/kg q8h	80 mg piperacillin/kg q8h	80 mg/kg q12h	4.5 g q6h
Tobramycin	2.5 mg/kg q8h	2.5 mg/kg q12h	2.5 mg/kg q24h	
TMP/SMX (Septra®) Oral preparations: single-strength tablet = 80 mg TMP; double- strength tablet = 160 mg TMP; oral suspension = 40 mg TMP/5 mL	<i>Mild to moderate systemic bacterial infection:</i> 5 mg/kg TMP q12h <i>Serious systemic bacterial infection:</i> 5 mg/kg TMP q6-8h <i>Pneumocystis jiroveci pneumonia prophylaxis:</i> 2.5 mg/kg TMP q12h three days per week	2.5 mg/kg TMP q12h 5 mg/kg TMP q8-12h 2.5 mg/kg TMP q12h three days per week	2.5-5 mg/kg TMP q24h 5 mg/kg TMP q12-24h 2.5 mg/kg TMP q24h three days per week	160 mg TMP bid three days/week
Vancomycin	15 mg/kg q6h <i>CNS infection:</i> 15-20 mg/kg q6h **Peak levels are not recommended. <u>Trough</u> levels (≤ 30 min before next dose) should be 5-20 mg/L depending on the severity of infection (e.g., goal trough = 15-20 for meningitis, sepsis and pneumonia)	15 mg/kg q8-12h 15-20 mg/kg q8h	15 mg/kg q12-24h 15-20 mg/kg q12h	

ANTI-FUNGALS				
Ambisome (liposomal amphotericin)	3-5 mg/kg q24h	No change Dosage reductions in renal disease are not necessary. However, due to the nephrotoxic potential of the drug, reducing the dose or holding the drug in the setting of a rising serum creatinine may be warranted. Use appropriate i.v. hydration & monitor daily creatinine and UOP.		
Caspofungin	load 70 mg/m ² , then 50 mg/m ² q24h	No change		
Fluconazole IV/PO	6-12 mg/kg/dose q24h <i>Fungal prophylaxis:</i> 3 mg/kg/dose q24h (give PO when able)	3-6 mg/kg q24h No change	3-6 mg/kg q24h No change	400 mg q24h
Voriconazole IV/PO (oral bioavailability > 95%)	load 6 mg/kg q12h x 2 doses, then 4 mg/kg q12h	No change IV voriconazole should be avoided in patients with CrCl<50 mL/min due to the accumulation of the IV vehicle and is contraindicated in ESRD		

ANTI-VIRALS				
Acyclovir IV	<i>Non-CNS HSV infection:</i> 5-10 mg/kg q8h	<u>25-50% of normal clearance</u> 5-10 mg/kg q12h <u>10-25% of normal clearance</u> 5-10 mg/kg q24h	2.5-5 mg/kg q24h	
	<i>Herpes zoster:</i> 10-20 mg/kg q8h OR 500 mg/m ² /dose q8h	<u>25-50% of normal clearance</u> 10-20 mg/kg q12h OR 500 mg/m ² q12h <u>10-25% of normal clearance</u> 10-20 mg/kg q24h OR 500 mg/m ² q24h	5-10 mg/kg q24h OR 250 mg/m ² q24h	
Ganciclovir IV	<u>>80% of normal clearance</u> 5mg/kg/dose q12h	<u>25-50% of normal clearance</u> 2.5 mg/kg q24h	1.25 mg/kg q24h	
	<u>50-79% of normal clearance</u> 2.5mg/kg/dose q12h	<u>10-25% of normal clearance</u> 1.25 mg/kg q24h		

For information regarding the dosing of antimicrobial agents in the setting of dialysis or hepatic failure, contact Infectious Diseases Pharmacy for further assistance.

ID Pharmacy Pager 443.9421

Normal serum creatinine concentrations at various ages

Age	Average Serum Creatinine (mg/dL)	Range (mg/dL)
Premature (<34 weeks GA)		
<2 weeks old	0.9	0.7-1.4
>2 weeks old	0.8	0.7-0.9
Term neonates (>34 weeks GA)		
<2 weeks old	0.5	0.4-0.6
>2 weeks old	0.4	0.3-0.5
2 weeks–5 years	0.4	0.2-0.5
5–10 years	0.6	0.3-1.0
>10 years	0.9	0.6-1.4

UCSF PEDIATRIC SUSCEPTIBILITY DATA (2008)

Gram-negative isolates (tested from all sites)

Organism	Total isolates	CZOL	CTRX	CTAZ	CFPM	GEN	TOB	T/S	CIP	P/T	IMI
<i>Acinetobacter baumannii</i>	1	N/A	0	100	100	100	100	100	100	N/A	100
<i>Citrobacter freundii</i>	5	N/A	60	60	100	60	80	40	100	60	100
<i>Enterobacter aerogenes</i>	3	N/A	100	100	100	100	100	100	100	100	100
<i>Enterobacter cloacae</i>	35	N/A	49	51	97	91	91	77	94	77	100
<i>Escherichia coli</i> *	77	84	94	92	97	90	88	60	94	88	100
<i>Klebsiella oxytoca</i>	9	22	44	100	100	89	89	67	100	44	100
<i>Klebsiella pneumoniae</i>	37	92	95	95	100	100	100	84	100	92	100
<i>Proteus mirabilis</i>	10	70	100	100	100	90	90	90	100	100	100
<i>Pseudomonas aeruginosa</i> **	39	N/A	N/A	92	82	92	100	N/A	82	95	82
<i>Serratia marcescens</i>	14	N/A	86	93	100	93	86	100	100	79	100

** *Pseudomonas aeruginosa* isolates do not include isolates from cystic fibrosis patients

- ◆ Anaerobes Routine antimicrobial susceptibility testing is not performed; results are not reproducible. *Bacteroides fragilis* universally produces β-lactamase.
- ◆ *Enterobacter* species Known to possess inducible cephalosporinase; resistance can emerge during cephalosporin therapy.
- ◆ **Escherichia coli* Outpatient cefazolin/cephalexin susceptibility is 91%. Outpatient TMP/SMX susceptibility is 74%. Outpatient ciprofloxacin susceptibility is 95%. Nitrofurantoin susceptibility is 99% and should only be used for uncomplicated UTIs in patients with CrCl >60 mL/min.
- ◆ *Haemophilus influenzae* National incidence of β-lactamase production is 37%.
- ◆ *Stenotrophomonas maltophilia* Routine antimicrobial susceptibility testing is performed on sterile sites and cystic fibrosis isolates. TMP/SMX is the most active agent against this organism.

Gram-positive isolates (tested from all sites)

Organism	Total Isolates	PCN	NAF	ERY	CLIN	CIP	DOX	T/S	VANC
<i>Staphylococcus aureus</i> *	147	6	73	45	78	69	95	97	100
<i>Staphylococcus epidermidis</i>	96	6	13	17	51	64	100	60	100
<i>Streptococcus pneumoniae</i>	26	See below	N/A	73	N/A	N/A	81	73	100

- ◆ **Staphylococcus aureus* Outpatient Nafcillin susceptibility 72% (Nafcillin resistance predicts cephalosporin resistance).
- ◆ *Enterococcus* species Majority of species are *Enterococcus faecalis* (100% AMP susceptible). *Enterococcus faecium* can be multi-drug resistant. Check vancomycin susceptibilities for all isolates from sterile sites. The addition of gentamicin (1 mg/kg Q8h) is required for bactericidal activity in serious systemic enterococcal infections. Of 25 enterococcal bacteremias in 2007, 1 was due to *Enterococcus faecium*, and no isolates were vancomycin resistant.
- ◆ *Streptococcus pneumoniae* **31% (8/26) of isolates were penicillin non-susceptible; 2/11 isolates intermediate & 2/11 resistant to CTRX. All isolates susceptible to levofloxacin.**

NOTE: For the treatment of meningitis, pending susceptibilities VANC empirically should be added to the regimen since failures (due to highly resistant isolates) have been reported with ALL third generation cephalosporins.

N/A = testing NOT APPLICABLE to organism. PIP = piperacillin, CZOL = cefazolin, CTRX = ceftriaxone, CTAZ = ceftazidime, CFPM = ceftazidime, GEN = gentamicin, TOB = tobramycin, T/S = trimethoprim/sulfamethoxazole, CIP = ciprofloxacin, IMI = imipenem, P/T = piperacillin-tazobactam, PCN = penicillin, NAF = nafcillin, ERY = erythromycin, CLIN = clindamycin, DOX = doxycycline, VANC = vancomycin, AMP = ampicillin

EMPIRIC ANTI-FUNGAL THERAPY

First line anti-fungal therapy remains liposomal amphotericin (Ambisome), although there is increasing evidence that voriconazole may be appropriate upfront therapy (must be wary of hepatic interactions/toxicity with common hepatotoxic chemotherapy agents such as methotrexate, though).

DIFFERING YEAST SUSCEPTIBILITY

Yeast	Amphotericin	Fluconazole	Voriconazole	Caspofungin
<i>Candida albicans</i>	+	+	+	+
<i>C. glabrata</i>	+	-	+/-	+
<i>C. kruseii</i>	+	-	+	+
<i>C. lusitania</i>	+/-	+/-	N/A	+
<i>C. parapsilosis</i>	+	+/-	N/A	+/-
<i>C. tropicalis</i>	+	+/-	N/A	+
<i>Cryptococcus</i>	+	+	+	-

DIFFERING MOLD SUSCEPTIBILITY

Mold	Amphotericin	Fluconazole	Voriconazole	Caspofungin
<i>Aspergillus</i>	+	-	+	+
<i>Rhizopus</i>	+	-	-	-

ANTIBIOTICS: GENERAL GUIDELINES

- 20% of patients with ANC <100 will have detectable bacteremia with fever
- Overwhelming infection is a major cause of mortality in oncology patients
- Factors contributing to increased infectious risk in children with cancer:
 - Neutrophils are a crucial line of defense against bacterial and fungal infections.
 - Malignancies themselves and chemotherapy agents cause defects in cell-mediated immunity.
 - Patients with leukemia are at particularly high risk of infections due to immune dysfunction sequelae, especially if these children are not in remission.
 - Mucous membrane and skin integrity may be disrupted from mucositis and from invasive procedures.
 - Most oncology patients have surgically implanted central catheters, which serve as reservoirs of infection.
 - Most patients are colonized with nosocomial pathogens.

Situations in which double antibiotic coverage are indicated:

- infection with *Pseudomonas* always
- infection with *Enterobacter* if neutropenic (if not neutropenic, single agent coverage is sometimes acceptable)
- infection with *Klebsiella* if neutropenic (if not neutropenic, single agent coverage is sometimes acceptable)

Situations in which cephalosporin monotherapy (except 4th generation, such as cefepime) are unacceptable [due to inducible cephalosporinase]:

- infection with *Enterobacter*
- some infections with *Citrobacter*, *Acinetobacter*, or *Serratia*

Positive *Staphylococcus aureus* or *Staphylococcus epidermidis* blood cultures:

- Assume MRSA! Never use penicillins first-line for *Staphylococcus epidermidis*; can change to nafcillin instead of vancomycin (bactericidal vs. bacteriostatic) for *Staphylococcus aureus* if cultures are sensitive (MSSA).
- Must call microbiology lab to request *Staphylococcus epidermidis* sensitivities be performed!

Central lines should always be promptly removed in the following situations:

- persistent bacteremia/line infection despite appropriate antibiotic coverage
- Hypotension or chills associated with use of line or persisting despite antibiotics
- infection with *Candida* species
- infection with *Bacillus* species
- line tunnel infection

CHEMOTHERAPY PRINCIPLES

Chemotherapy roadmaps are generally entered into the Foxpro database by the patient's primary oncologist (fellow, or attending when there is no fellow). The chemotherapy orders are printed out on special order sheets by the nurse practitioners, along with fluid, anti-emetic and other planned supportive care orders.

All chemo orders must have **2 signatures** to be processed by the pharmacy. Each signature must include 5 digit ID#, date and time. The first signature is typically a fellow or nurse practitioner, but can also be a pharmacist (NO residents). An attending must give the final signature & must time it last. Before signing, review the following items:

- Roadmap (doses and schedule) must be checked against the protocol if patient is being treated per a protocol or with the primary fellow & attending if not.
- The Roadmap must reflect the exact order that you wish to prescribe. Often, "as per" protocol Roadmaps need to be built to reflect any changes that deviate significantly from the original protocol (e.g. changing an adriamycin infusion from CI/24hrs to bolus)
- If there is a change in the order from what the Roadmap states, there must be a note on the Roadmap in the Treatment Notes section (e.g. dose reduction, length of infusion change, etc.)
- Review the checklist of required pre-chemo lab tests and studies listed in the protocol to make sure that the patient received all that are indicated and that it is safe for the patient to start this round of chemotherapy.
- Review the patient's past medical history against the chemotherapy protocol to make sure that no dose modifications are required. Problems that may require dose modifications include: allergies, prolonged low counts, abnormal creatinine clearance (see Schwartz formula below), abnormal transaminases or bilirubin, severe peripheral neuropathy, severe mucositis, cardiac echo, etc.
- The formula below must be used to calculate body surface area (BSA) from the most recent height and weight and this number used to verify (by recalculation) drug dosing for every drug ordered. If the BSA has changed, and the difference between calculated drug dose and ordered drug dose is $\geq 10\%$, the roadmap and chemotherapy orders must be rewritten.
- In young or small children (typically under the age of 3), many chemotherapy drugs are weight-based, rather than BSA-based. The same rules regarding dose verification. Check carefully what is appropriate for such patients, as the doses will be very different (~25% lower) if mg/kg dosing used instead of BSA dosing!
- Review supportive care guidelines listed in the chemotherapy protocol and verify fluid and other supportive care orders.

BODY SURFACE AREA

$$\text{BSA} = \text{Square root of } \frac{\text{height (cm)} \times \text{weight (kg)}}{3600}$$

Creatinine clearance (Schwartz formula)

$$C_{Cr} = \frac{K \times \text{height (cm)}}{P_{Cr}}$$

K	Age
0.45	Infant
0.55	Child
0.55	Teen Girl
0.7	Teen Boy

The following lists some of the more common problems caused by chemotherapy and tips on dealing with them. It is by no means an exhaustive list.

- **Asparaginase (L-asparaginase, PEG-L-asparaginase, *Erwinia*)** can cause allergic reaction, hyperglycemia, pancreatitis, hypofibrinogenemia, thrombosis, hemorrhage, and (rarely) hemorrhagic cystitis. Treat allergy to L-asparaginase with Benadryl and possibly steroids; add epinephrine for anaphylaxis. Switch to *Erwinia* form for the next dose. Dip urine for glucose. If positive, obtain serum glucose and urine ketones. If those are elevated, remove glucose from IVF. If hyperglycemia is severe or persistent, consider adding insulin after discussion with fellow or attending.
- **Cisplatin** can cause severe nausea and vomiting, is nephrotoxic, and causes magnesium wasting. Aggressive antiemetics should be ordered, along with hydration, mannitol and magnesium supplementation. Avoid concomitant nephrotoxic and ototoxic drugs when possible.
- **Cyclophosphamide** and **ifosfamide** can cause hemorrhagic cystitis. Follow urine dips for blood and make sure patient meets urine output parameters. If urine dip positive, send for microscopic analysis, stop chemo, and increase fluids. Mesna is commonly used as a uro-protectant. It is a ketone, so expect ketonuria on dips.
- **Cytarabine (ara-C)** can cause a “flu-like” syndrome with fevers, chills, hypotension. Ara-C (>1gm/m²) often causes a chemical conjunctivitis. Use decadron ophthalmic eye drops around the clock to prevent/lessen. High dose Ara-C is associated with mucositis and Strep viridans bacteremia. Include vancomycin in the antibiotics.
- **Dactinomycin (actinomycin-D)** is frequently associated with “radiation recall”. Watch for skin reddening, rash, or pain in areas of previous radiation.
- **Daunorubicin** and **doxorubicin (Adriamycin)** are cardiotoxic and can be associated with congestive heart failure or arrhythmias. If a patient complains of chest pain or dyspnea, get an EKG and CXR. Adriamycin can cause a red/orange

discoloration of the urine, which is normal. They are also associated with “radiation recall.”

- **Ifosfamide** requires adequate hydration and strict attention to urine output parameters. Mesna is usually used for uroprotection. A metabolite of ifosfamide is neurotoxic and can cause mental status changes, somnolence, seizures, etc. If any of these symptoms occur, stop the infusion and then call the fellow or attending for further advice.
- High-dose **methotrexate** ($>3\text{gm/m}^2$) can cause renal damage if patients are not alkalinized and well-hydrated. In addition, profound cytopenias and mouth sores can develop if patients are not taking adequate doses of leucovorin (see Methotrexate section). Monitor the serum methotrexate level and creatinine per protocol until MTX $<0.1\mu\text{mol}$.
- **Vincristine** is often associated with peripheral neuropathies, jaw pain, and constipation. It can also cause SIADH. Monitor urine and stool output.
- **VP-16 (etoposide)** can cause hypotension and allergic reactions. Infuse slowly and monitor blood pressure during and after the infusion.

GUIDELINES FOR PATIENTS RECEIVING HIGH DOSE METHOTREXATE

Patients with osteosarcoma and ALL commonly receive high-dose (≥ 4 grams/m²/dose) methotrexate. Safe administration of high-dose methotrexate requires careful attention to hydration, urinary alkalinization, blood methotrexate levels, creatinine and timely initiation of leucovorin (folate) rescue. The goal urine pH is 7-8 to promote clearance.

Concomitant Medications to Avoid

Check to make sure patient is not taking medications that interfere with methotrexate clearance or protein binding. Hold the following medications on the day of infusion and for at least 72 hours after the start of methotrexate until level <0.1 uM

- Salicylates
- Ibuprofen
- Sulfa (e.g., Septra or Bactrim)
- Penicillins
- Vitamin C
- Phenytoin
- Proton pump inhibitors (e.g., omeprazole, lansoprazole, etc.)

Methotrexate and creatinine levels:

ALL LEVELS ARE TIMED FROM THE START OF THE METHOTREXATE INFUSION. Methotrexate levels are run in the morning currently at 1000 (results back in the early afternoon), regardless of the time they are drawn.

Osteosarcoma

Patients with osteosarcoma typically receive 12 grams/m²/dose (rounded up to nearest gram) methotrexate given IV over 4 hours. The maximum dose is typically 20 grams. Patients receive their methotrexate after they have met urine specific gravity and urine pH requirements. This is accomplished through pre-hydration with bicarbonate containing IV fluids to promote renal excretion of the drug.

Hydration continues until blood methotrexate level is ≤ 0.1 micromolar.

Leucovorin rescue with 15 mg IV or PO starts 24 hours after the start of methotrexate infusion and usually continues every 6 hours until blood methotrexate level is ≤ 0.1 micromolar.

Patients have methotrexate levels and creatinine levels drawn at hour 4, 24, and then each morning. These values help guide whether a patient is clearing methotrexate more slowly and are therefore at increased risk of toxicity.

Patients typically remain admitted to the hospital until they have “cleared” their methotrexate (methotrexate level ≤ 0.1 micromolar), even if taking PO leucovorin.

The following are the current COG osteosarcoma guidelines for patients with delayed excretion as well as mild, moderate and severe toxicity. **Any concern of toxicity or delayed clearance should prompt discussion with the fellow and attending:**

Delayed excretion: If methotrexate level $> 0.1 \mu\text{M}$ at 72 hrs, recheck level at 96 hrs. Discontinue leucovorin and fluids if $< 0.08 \mu\text{M}$ at 96 hrs. If not, discontinue when level is $< 0.05 \mu\text{M}$.

Mild toxicity: Methotrexate levels above shaded area in nomogram but below first solid line, creatinine increase of 25-50%; grade I-II stomatitis.

Intervention: Increase hydration, usually to $200 \text{ mL/m}^2/\text{hr}$

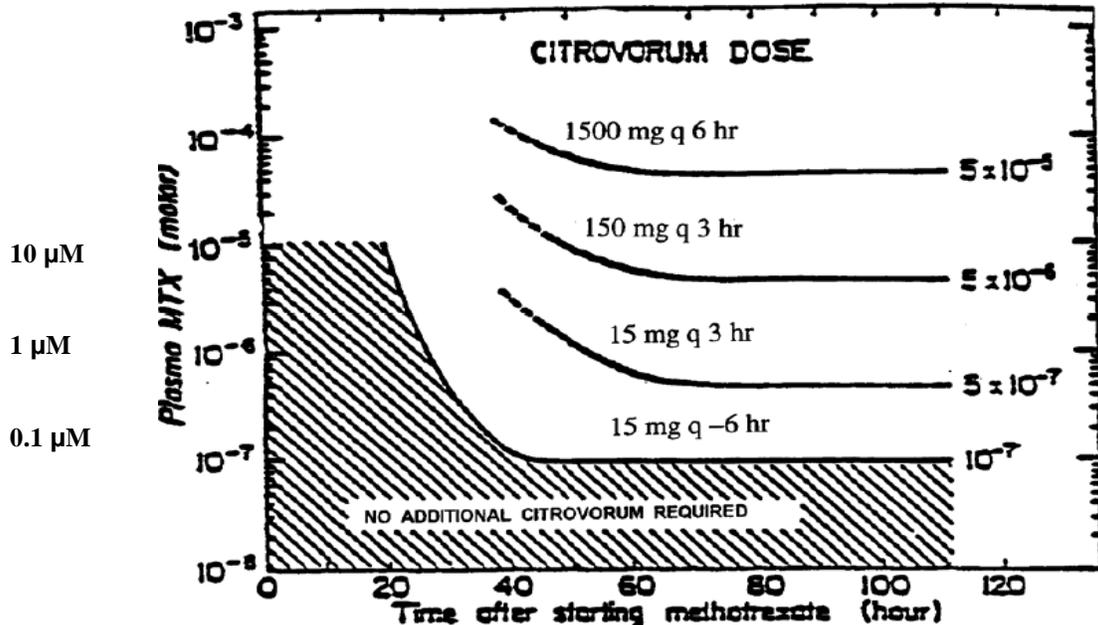
Moderate toxicity: Methotrexate levels above shaded area in nomogram but below first solid line, creatinine increase of 50-100%, grade III-IV stomatitis or myelosuppression on current or previous course.

Intervention: Increase hydration, usually to $200 \text{ mL/m}^2/\text{hr}$. Increase leucovorin to 15 mg q3h until criteria for discontinuing leucovorin reached

Severe toxicity: Methotrexate levels above solid line, i.e., $> 50 \mu\text{M}$ at 24 hours or $> 5 \mu\text{M}$ at 48 hrs or $> 100\%$ increase in serum creatinine

SEVERE TOXICITY REQUIRES PROMPT INTERVENTION! In cases of severe methotrexate toxicity, increase hydration and leucovorin immediately. In addition, call the Pharmaceutical Management Branch at 301-496-5725 for information on obtaining **carboxypeptidase** (which breaks down methotrexate), available via an NCI Special Exception Use Protocol.

Nomogram for Leucovorin (Citrovorum) Dosing after Methotrexate 12 grams/m^2



Acute Lymphoblastic Leukemia (ALL)

Patients with high-risk ALL typically receive 5 grams/m²/dose methotrexate IV.

Patients with infant ALL typically receive 4 grams/m²/dose methotrexate IV.

Methotrexate level cutoffs are different for each protocol.

AALL0232: High Risk B-precursor ALL

Dose: 5000 mg/m²/dose

Administration: Methotrexate 500 mg/m² is given over 30 minutes.

Methotrexate 4500 mg/m² is given over 23.5 hours.

Monitoring: Urinalysis: urine pH goal 7-9; urine spec gravity goal ≤ 1.010

Methotrexate level, creatinine: Hours 24, (36 if needed), 42, 48, then qAM

What to do (see also Appendix III in AALL0232 protocol)

Hour 24 levels:

If MTX < 150 uM, continue standard hydration, check levels at hour 42

If MTX ≥ 150 uM or Cr > 125% baseline,

1. repeat level now if MTX contamination is possible
2. increase hydration to 200 mL/m²/hr
3. draw 36 hour MTX and creatinine

Hour 36 levels (draw **only** if elevated hour 24):

If MTX ≤ 3 uM, resume standard hydration at 125 mL/m²/hr

If MTX > 3 uM, continue hydration at 200 mL/m²/hr

If MTX > 10 uM, continue hydration at 200 mL/m²/hr

consider carboxypeptidase

Hour 42 MTX ≤ 1 uM	Hour 48 MTX ≤ 0.4 uM	Hydration Continue standard hydration at 125 mL/m ² /hour	Leucovorin Rescue At hour 42, start leucovorin 15 mg IV/PO q6 hours (ie give dose at hour 42, 48, 54 etc) until MTX < 0.1 uM **if patient had high levels at Hour 36 or 42 but then levels return to expected, may resume standard hydration of 125 mL/m ² /hr (if satisfactory urine output)
1.01 – 9.9 uM	0.41 – 5.9 uM	Increase to 200 mL/m ² /hour	At hour 42, start leucovorin 15 mg IV/PO q6 hours (ie give dose at hour 42, 48, 54, etc) until MTX < 0.1 uM Draw levels q12-24 hr
≥ 10 uM	≥ 6 uM	See Protocol	See Protocol

AALL0631: Infant ALL

Dose: 4000 mg/m²/dose

Administration: Methotrexate 200 mg/m² is given over 20 minutes.
Methotrexate 3800 mg/m² is given over 23.7 hours.

Monitoring: Urinalysis: urine pH goal 7-9; urine spec gravity goal ≤ 1.010
Methotrexate level, creatinine: Hours 24, (36 if needed), 42, 48, then qAM
Perineum (these babies require foley catheters to protect their skin)

What to do (see also protocol guidelines)

Hour 24 levels:

If MTX < 150 uM, continue standard hydration, check levels at hour 42

If MTX ≥ 150 uM or Cr > 125% baseline:

1. Increase hydration to 200 mL/m²/hr
2. Draw 36 hour MTX and creatinine
3. repeat level now if MTX contamination is possible

Hour 36 levels (draw **only** if elevated hour 24):

If MTX ≤ 3 uM, resume standard hydration at 125 mL/m²/hr

If MTX > 3 uM, continue hydration at 200 mL/m²/hr

If MTX > 10 uM, continue hydration at 200 mL/m²/hr

consider carboxypeptidase

Hour 42 MTX level ≤ 9.9 uM	Hour 48 MTX level < 5.9 uM	Hydration Continue standard hydration at 125 mL/m ² /hour	Leucovorin Rescue Leucovorin 15 mg/m ² IV q6 hours (ie give dose at hour 42, 48, 52, etc) until MTX < 0.1 uM
10 – 39.9 uM	6 – 19.9 uM	Increase to 200 mL/m ² /hour	Leucovorin 15 mg/m ² IV q3 hours (ie give dose at hour 42, 45, 48 , etc) until MTX < 0.1 uM Draw levels q6-24 hr Consider carboxypeptidase
≥ 40 uM	≥ 20 uM	See Protocol	See Protocol

POG9310: Relapsed ALL protocol using intermediate-dose methotrexate, so urine pH and specific gravity requirements are more liberal.

Administration: Methotrexate 200 mg/m² is given as IV push
Methotrexate 800 mg/m² is given over 24 hours.

Monitoring: Urinalysis: urine pH goal ≥ 6.5; urine spec gravity goal < 1.015
Methotrexate level, creatinine: Hour 24 then qAM
See protocol document for further details.

MENSTRUAL BLEEDING

(Note: text is from 2005; update is pending)

Ortho-Novum 1 + 35 (21 day pack with no placebo) can stop menstrual flow at high doses, but does not protect ovaries and should not be given long-term without a break. Depo-Lupron may offer ovarian protection and can be used for long-term suppression. Patient must be on Ortho-Novum for a week or more before starting Lupron.

If bleeding at admission: Order 3 packs of Ortho-Novum 1 + 35 (21 day pack with no placebo)

1. First part: Start Ortho-Novum 1 + 35 (21 day pack with no placebo). If light bleeding, 2 pills qday x 7 days; if heavy bleeding, 3 pills qday x 7d. (This dosage may induce nausea. An antiemetic may be used).
2. Second part: Taper Ortho-Novum 1 + 35 by one pill. 2 pills (or 1 pill for light bleeding) qd x 10days. Start depo-Lupron (GnRH agonist) 11.25 mg IM q3months.
3. Third part: Taper Ortho-Novum to one pill qday x 21 days.

If not bleeding at admission

1. Start Ortho-Novum 1 + 35 pills (21 day pack with no placebo) 1 tab qday x 21 days.
2. After 1 week of Ortho-Novum, start depo-Lupron (GnRH agonist) 11.25 mg IM q3months.

If long-term (>3 months) suppression is sought

1. Continue Depo-Lupron q 3 months for 2 months post-chemo
2. Add Prempro [estrogen] (0.625 CEE/2.5 MPA) during the 1st month after cessation of OCPs as above.
3. Continue Prempro until Lupron is discontinued.

Benefits of Lupron over Provera:

- 1) Potential ovarian protection during chemotherapy
- 2) Can counteract adverse symptoms (hot-flashes or depression) by adding back estrogen

ONCOLOGIC EMERGENCIES

Types of Emergencies

1. Cardiothoracic emergencies
 - a. Superior vena cava syndrome (SVCS)/Superior mediastinal syndrome
 - b. Malignant pericardial/pleural effusion
 - c. ATRA syndrome
2. Neurologic emergencies: spinal cord compression
3. Abdominal emergencies: typhlitis
4. Urologic emergencies: hemorrhagic cystitis
5. Hematologic emergencies
 - a. Hyperleukocytosis
 - b. DIC
 - c. Cytopenias – see transfusion guidelines
6. Life-threatening metabolic disturbance
 - a. Tumor lysis syndrome
 - b. Hypercalcemia
7. Infectious emergencies – see fever guidelines
8. Pain – see pain guidelines

Superior vena cava syndrome (SVCS) and superior mediastinal syndrome (SMS)

- SVCS: compression of the SVC by mass, or occlusion by thrombus, impeding blood return to heart
 - SMS: tracheal compression by extrinsic anterior or posterior mediastinal mass (i.e. in leukemia/lymphoma/germ cell tumors)
1. Presentation
 - a. Signs: facial/neck swelling, plethora, cyanosis of face, neck, and upper arms, diaphoresis, engorged veins on chest wall, wheezing, and stridor.
 - b. Symptoms: cough, dyspnea, orthopnea, headache, anxiety, feeling full in ears, lethargy, visual disturbances, syncope. Acuity of symptoms gives clues about acuity of tumor. (Hodgkin's more indolent, lymphoblastic lymphoma much more acute.)
 - c. Increased SOB lying supine or prone, or low room air O2 sat are signs of concern
 - d. *If respiratory failure lying supine, sit patient up!*
(May also be more comfortable prone)
 2. Evaluation
 - a. CXR, PA & lateral: presence of mass, mediastinal widening, tracheal deviation
 - b. Chest CT with and without contrast (essential to have contrast to visualize the vessels in the mediastinum, and helps to visualize tracheal diameter)
 - i. If tracheal cross-sectional area (TCA) <50% predicted for age and gender, avoid anesthesia
 - c. ECHO
 - i. May pick up clots (but not gold standard)
 - ii. Evaluation for tamponade or tamponade effects

- d. PFTs
 - i. If peak expiratory flow in supine position <50% predicted for age, avoid anesthesia
3. *Critical airway: TCA<50% predicted, PEF<50% pred, significant narrowing of mainstem bronchi, or respiratory distress or failure*
4. Making a diagnosis in setting of critical airway
 - a. Attempt diagnosis in least invasive manner possible (peripheral blood > bone marrow bx > pleural fluid thoracentesis > bx of palpable node under local anesthesia > mediastinal bx under local anesthesia)
 - b. If impending respiratory failure, may need to treat without establishing a diagnosis
5. Treatment
 - a. Emergent treatment of SVCS/SMS due to tumor:
 - i. Chemotherapy – steroids
 1. Radiation -- recognize that XRT may cause local swelling
 - b. Clot: anticoagulation or thrombolysis

Pleural/Pericardial Effusions

- Exudates from local invasion or metastatic spread of tumor
 - Blood from hemorrhage of tumor or erosion of CVL into pleura or pericardial sac
1. Presentation – acute accumulation worse than gradual.
 - a. Signs: cardiopulmonary failure, shock, cyanosis, friction rub, diastolic murmurs, pulsus paradoxus>10mm. Pulsus>20mm represents severe tamponade.
 - b. Symptoms: SOB, anxiety, chest pain, hiccups
 2. Imaging
 - a. CXR: evaluate amount of pleural fluid present, lateral/decubitus
 - b. EKG: may demonstrate flattening of t-waves or decreased voltage
 - c. ECHO: confirm effusion and evaluate for hemodynamic compromise, tamponade physiology
 3. Diagnosis
 - a. If new tumor, thoracentesis can alleviate symptoms and make diagnosis
 - b. Pericardial tap to alleviate symptoms and hemodynamic compromise
 4. Treatment
 - a. Remove fluid if clinically significant
 - b. Treat tumor if effusion is tumor-related.
 - c. Maintain intravascular volume if pericardial effusion present (i.e. no diuretics)

ATRA Syndrome

Differentiation syndrome seen in patients with acute promyelocytic leukemia on induction course of ATRA (all-*trans* retinoic acid)

1. Presentation
 - a. Usually occurs in first and third weeks after starting ATRA
 - b. WBC > 5,000 is risk for more severe disease
 - c. Symptoms: SOB, dyspnea, feeling unwell

- d. Signs: Fever, dependent edema, weight gain, pleural and pericardial effusions, hypotension, rash, acute renal failure
- 2. Imaging: pulmonary infiltrates in 80%
- 3. Diagnosis: constellation of clinical signs and symptoms with ATRA use
- 4. Treatment: **ATRA syndrome can be rapidly fatal if not recognized!**
 - a. Hold ATRA!
 - b. Decadron, 0.25 mg/kg/dose BID for children < 40 kg
10 mg/dose for children or adults > 40 kg

Spinal Cord Compression

OCCURS IN 4% OF CHILDREN WITH CANCER (SARCOMA, NEUROBLASTOMA, LEUKEMIA, LYMPHOMA, METASTATIC BRAIN TUMORS)

- 1. Presentation – need to ask about weakness, bowel/bladder function
 - a. Signs: Tenderness to percussion over involved area is a very reliable localizing sign, loss of strength in extremities with distal strength being relatively more well preserved than proximal strength, sensory losses, hyperreflexia, loss of anal tone or wink
 - b. Symptoms: back pain, progressive weakness, bowel/bladder dysfunction, “ataxia” from lower extremity weakness
- 2. Diagnosis
 - c. Immediate urgent Spinal MRI +/- gadolinium most useful for delineating anatomy and extent of compression
- 3. Treatment
 - d. Get diagnostic tissue ASAP if new tumor
 - e. Decadron, 0.25 mg/kg x1, then 0.1 mg/kg IV STAT
 - f. Neurosurgery and Radiation Oncology consults STAT
 - g. Chemotherapy usually indicated for new sarcoma/neuroblastoma/lymphoma unless patient presents with flaccid paralysis
 - h. Radiation therapy can be given in almost any situation while awaiting diagnosis to decide on chemotherapy
 - i. Remember: the earlier you treat, the more likely it is that the patient will regain function

Typhilitis – Neutropenic colitis

- 1. Presentation
 - a. Signs: fever (not always), neutropenia, bleeding from gut, shock, sepsis, vomiting, peritoneal rigidity (implying infarction)
 - b. Symptoms: pain, nausea, bloating
- 2. Diagnosis
 - a. CT scan with oral contrast to see bowel wall edema & pneumatosis intestinalis
 - b. U/S
 - c. KUB to look for thumbprinting
- 3. Treatment
 - a. NPO, large NG tube to LIS (ensure platelets adequate, usually >50,000)
 - b. Surgical consult to follow along

- c. Triple antibiotic coverage – usual pathogens are GNRs
- d. TPN (controversial)
- e. Fluids and pressors as necessary

Hemorrhagic Cystitis

1. Pathophysiology
 - a. Usually preceded by chemotherapy with cyclophosphamide or ifosfamide
 - b. Can happen hours to years after administration of chemotherapy
 - c. Caused by acrolein (drug metabolite) accumulation in bladder
2. Presentation
 - a. Signs: gross hematuria, clots
 - b. Symptoms: dysuria
3. Treatment
 - a. Platelets if low
 - b. Irrigation with 3-way Foley in children big enough to sustain Foley
 - c. IV hydration
 - d. Prostaglandin E infusions?
 - e. Ditropan for symptom management

Hyperleukocytosis

1. Definition: peripheral WBC > 100,000. AML > ALL
2. Pathophysiology: leukemia cells have increased adhesion causing high viscosity and can sludge in CNS, lungs, renal vessels, etc. This complication of hyperleukocytosis is called leukostasis. Not all patients with hyperleukocytosis will have leukostasis.
3. Symptoms of leukostasis are varied and can include lethargy, stroke findings, head bleeds, respiratory distress
4. Treatment:
 - a. Hydration with D5 1/4 NS + 40 mEq NaHCO₃ @ 2x maintenance
 - b. Allopurinol
 - c. Consider leukopheresis for AML with WBC > 100,000. ALL – no clear guidelines, but any patient with any clinical symptoms of hyperleukocytosis should be pheresed
 - d. Keep platelets > 20,000
 - e. Do not transfuse hgb > 10 gm/dL because it may increase viscosity
 - f. Begin chemotherapy ASAP

Disseminated Intravascular Coagulation

Excessive activation of coagulation and consumption of clotting factors

1. Presentation
 - a. **elevated PT & aPTT**
 - b. **thrombocytopenia**
 - c. **hypofibrinogenemia**
 - d. **elevated d-dimers & fibrin split products**
 - e. **Particularly common in acute promyelocytic leukemia (APL)**
2. Treatment
 - a. Treatment of underlying etiology

- b. Supportive therapy
- c. Thrombocytopenia: platelet transfusion
- d. Hypofibrinogenemia: cryoprecipitate (1 unit/5-10kg)
 - f. Coagulopathy: low-dose heparin therapy (7.5 units/kg/hr IV)
 - g. Hyperfibrinolysis (low anti-plasmin levels): e-aminocaproic acid (100 mg/kg i.v. or p.o. q6h)

Tumor Lysis Syndrome

- constellation of metabolic abnormalities caused by release of intracellular contents during massive cell breakdown, leading to hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and elevated creatinine
- i) Presentation: Most common in Burkitt's lymphoma, T-cell ALL, some AML, but may happen with any tumor. Timing is generally at presentation or within 72h of initiating cytotoxic chemotherapy.
 - Laboratory definition (2 or more):
 - Uric acid \geq 8 mg/dL, or 25% increase from baseline
 - K⁺ \geq 6 mEq/L, or 25% increase from baseline
 - Phos \geq 6.5 mg/L, or 25% increase from baseline
 - Ca \leq 7 mg/dL, or 25% decrease from baseline
 - Clinical definition
 - Creatinine \geq 1.5 x upper limit normal
 - Cardiac arrhythmia or sudden death
 - Seizure
- ii) Pathophysiology: Lysis of tumor cells and release of contents (potassium, phosphorous, nucleic acids) into bloodstream. Purine nucleic acids \rightarrow hypoxanthine \rightarrow xanthine \rightarrow uric acid (by xanthine oxidase). Uric acid crystallizes within renal tubules, causing renal failure. Hyperkalemia causes cardiac arrhythmias. Hyperphosphatemia leads to hypocalcemia and seizures. Calcium phosphate product $>$ 70 increases risk for calcium phosphate precipitation within renal tubules, exacerbating problem.
- iii) Prevention/Treatment: Goal is to keep electrolytes normal & prevent renal failure
 1. Adequate hydration and diuresis
 - a. D5 1/4NS + 40-50 mEq NaHCO₃ to alkalinize urine
 - i. Keep urine pH 7-7.5 to prevent precipitation of uric acid stones (at low pH) and Ca₂PO₄ stones and hypoxanthine (at high pH)
 - ii. Do not need to alkalinize fluids when using rasburicase
 - b. Keep Is & Os relatively balanced. Use diuretics with caution.
 - c. Avoid adding K⁺ or Ca²⁺ to fluids (unless iCa critically low)
 - d. Dialyze if anuric and in renal failure
 - e. Treat hyperkalemia and hyperphosphatemia
 2. Allopurinol (xanthine oxidase inhibitor) to block formation of uric acid
 - Children \leq 10 years:
 - IV: 200 mg/m²/day in 1-3 doses (max 600 mg/day)
 - Oral: 10 mg/kg/day in 2-3 doses or 200-300 mg/m²/day in 2-4 doses (max 800 mg/day)

Children $>$ 10 years & adults:

IV: 200-400 mg/m²/day in 1-3 doses (max 600 mg/day)

Oral: 600-800 mg/day in 2-3 doses

Adjust dose for renal insufficiency

3. Rasburicase (urate oxidase) to break down uric acid

- Consider use in patients at high risk for TLS (Burkitt's, ALL with WBC > 100,000, AML with/ WBC > 50,000) or those who show clinical or laboratory evidence of TLS
- Dose = 0.15-0.2 mg/kg/dose daily as needed based on uric acid level, up to 5 days
- Contraindicated in patients with G6PD deficiency (risk of hemolytic anemia)

4. Follow electrolytes q6-8 hours as necessary, particularly after starting first chemotherapy. Uric acid levels should be monitored at least every 12 hours while patient is receiving rasburicase.

- Send STAT in gold top or light green top **on ice** (rasburicase will cause enzymatic degradation of the uric acid in blood samples left at room temperature, resulting in spuriously low uric acid levels)
- Designate "rasburicase therapy" on lab slip for uric acid

5. Electrolyte abnormalities

a. Hyperphosphatemia

- Moderate (>2.1 mmol/L): phosphate binder such as Aluminum hydroxide 50-150 mg/kg/d divided q6h PO or NG (max 1-2d)
- Severe: dialysis

b. Hyperkalemia: send stat repeat and obtain EKG

- > 6 mmol/L and asymptomatic: Kayexalate (PO)
- > 7 or symptomatic (wide QRS):
 - Regular insulin 0.1 units/kg + D25 (2mL/kg) IV
 - Na bicarb 1-2 mEq/kg
 - Calcium gluconate 100-200 mg/kg/dose

c. Hypocalcemia

- Symptomatic: Calcium gluconate 50-100 mg/kg

Hypercalcemia

i) Presentation: can be a neoplastic syndrome seen in ALL, NHL, NB, Ewing's. Also can be a complication of cis-Retinoic acid (Accutane) therapy.

Symptoms: anorexia, nausea, vomiting, polyuria, diarrhea

ii) Treatment:

1. Correct dehydration and electrolyte abnormalities

2. Hydration & diuresis: NS @ 2x maintenance & furosemide (once dehydration corrected) @ 1-2 mg/kg IV q6h

3. Bisphosphonates (block osteoclastic bone resorption): pamidronate 1-2 mg/kg IV infused over 4h; may repeat x 1 in one week

4. Calcitonin 0.5-1 unit/kg IM or SQ daily

5. Prednisone 1-2 mg/kg PO daily (hematologic malignancy)

6. Dialysis

References:

Coiffier B et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *J Clin Oncol* 2008; 26(16): 2767-2778.

Halfdanarson TR et al. Oncologic Emergencies: Diagnosis and Treatment. *Mayo Clin Proc.* 2006; 81(6):835-848.

Montesinos P et al. Differentiation syndrome in patients with acute promyelocytic leukemia treated with all-*trans* retinoic acid and anthracycline chemotherapy: characteristics, outcome, and prognostic factors. *Blood* 2009; 113(4): 775-783.

Pergler L et al. Management of children and adolescents with a critical airway due to compression by an anterior mediastinal mass. *J Ped Surg* 2008; 43(11): 1990-1997.

NEW LEUKEMIA DIAGNOSIS

ALL is the most common childhood cancer, and patients with newly-diagnosed leukemia often are admitted in the middle of the night! The on-call fellow will advise you and will come in to see the patient, but these are guidelines to facilitate the initial evaluation of a new patient with a likely diagnosis of leukemia. Trust your instincts – if the patient seems very ill or has markedly abnormal laboratory studies, imaging, or vital signs, he/she may need a higher level of care in the PICU.

Initial evaluation:

- Obtain full history & physical exam:
 - Ask specifically about bleeding (epistaxis, gingival bleeding, hematuria, melena) and bruising symptoms, headache, fatigue, bone pain, sick contacts, etc.
 - Obtain a detailed family history of others with childhood and adult cancers, bleeding diatheses, genetic syndromes, and other problems
 - Examine the patient from HEAD TO TOE! This includes fundoscopic exam (look for leukemic infiltrates), oral exam (look for lesions, gingival hypertrophy, tonsils), full lymphatic exam (cervical, supraclavicular, axillary, and inguinal nodes), cardiac, respiratory, abdominal (assess for hepatomegaly, splenomegaly, other masses, bowel sounds), GU (must palpate all testes to assess for masses or asymmetry), extremities, complete dermatologic exam (assess bruising, petechiae, rashes), neurologic exam including cranial nerves, etc.
 - Ask RN to measure patient's height and weight! Most chemotherapy is dosed based on body surface area (sometimes mg/kg dosing for infants). Intrathecal chemotherapy dosing is age-based.
- Assess vital signs & known outside hospital labs.

Imaging:

- Order 2-view CXR to assess for mediastinal mass, cardiomegaly, and pulmonary leukemic infiltrates. Be sure to get a good quality image in the Radiology suite if patient is stable to leave 7 Long.
- Patients with AML and high-risk ALL (WBC >50,000 and/or age \geq 10 years) need a baseline echocardiogram prior to starting chemotherapy.
- For patients with hyperleukocytosis and altered mental status, consider head CT (to assess for thrombosis) if clinically stable to leave PICU.

Labs:

- **STAT** CBC with differential. Alert hematology lab (353.1747) about potential new leukemia diagnosis and ask to make peripheral blood smear ASAP to review. The fellow and resident should look at smear together in Hematopathology lab (M524).
- **STAT** coags: PTT/PT/fibrinogen +/- d-dimers (T cell leukemia and acute promyelocytic leukemia commonly present with coagulopathy)
- **STAT** type and cross: most patients need blood products

- **STAT** tumor lysis labs: chem-10 (electrolytes, Ca/Mg/P, BUN/Cr), LDH, and uric acid
- LFTs: AST, ALT, total/direct bilirubin, alkaline phosphatase, GGT, albumin
- Infectious serologies: HSV-1, HSV-2, CMV, EBV, VZV (IgGs); hepatitis A antibody, hepatitis B surface antigen and surface & core antibodies, HIV antibodies
- TPMT polymorphism testing (specify “send to Quest”)
- Place PPD (no controls necessary per Dr. Weintrub/Infection Control) and read at 48-72 hours.

Determine frequency of tumor lysis labs with fellow pending initial results (usually q4-q8 hours at first) and underlying diagnosis. Remember that the rate of change in labs is just as critical as the abnormalities!

Fluids and Medications:

- Order alkalinized fluids to manage/prevent tumor lysis syndrome: D5 ¼ NS + 40-50 mEq/L NaHCO₃ @ 1.5-2 times maintenance (discuss with fellow) for patients >12 kg who do not have significant fluid sensitivity issues. **Never put potassium in fluids!** Follow urine pH (point of care RN testing) qvoid and adjust NaHCO₃ prn to maintain urine pH 7-8.
- Order allopurinol 10 mg/kg/day p.o. divided q8h to facilitate uric acid excretion. Round dose to nearest 25 or 50 mg (due to tablet size). Never give allopurinol i.v. – can cause serious anaphylaxis. More rarely, patients with extremely high uric acid levels (e.g., >10), hyperleukocytosis, and Burkitt’s lymphoma will get rasburicase (recombinant urate oxidase; \$\$\$\$) 0.2 mg/kg q24h -- must discuss with fellow. Any patient receiving rasburicase should NOT receive alkalinization of fluids (change to D5 ½ NS @ 1.5-2 times maintenance), and all uric acids levels must be sent STAT and ON ICE.
- Febrile patients should have blood cultures obtained q24h and be put on appropriate systemic antibiotics. All new leukemia patients are considered high-risk regardless of blood counts (those WBCs don’t work properly). Recall that leukemia itself can cause fever, but cannot exclude infection.

Procedures:

- Patient will undergo bone marrow aspiration and lumbar puncture to determine definitive diagnosis. (Fellow will consent family to procedures and order chemotherapy.) Don’t forget to make NPO! Leukemia diagnosis can often be made from peripheral blood by flow cytometry if there are circulating blasts. The fellow will help to coordinate this sample and testing.
- Consider calling Pediatric Surgery resident to provide heads-up about new leukemia diagnosis. New leukemia patients require central catheter placement (usually Port-a-cath for ALL and double-lumen Broviac for AML). If diagnosis is certain, we try to coordinate line placement with bone marrow and LP. The fellow will book OR otherwise for diagnostic procedures. If diagnosis not definitive or if unable to coordinate with Surgery, alert PICC RN for PICC placement once leukemia diagnosis is confirmed so that the

patient can start chemotherapy promptly. (Patients with initial PICCs will undergo definitive central line placement by Pediatric Surgery at the end of induction chemotherapy once off steroids and when ANC recovered.)

PAIN: TREATMENT GUIDELINES

- Always believe your patient!
- Along with treating the pain, remember to search for the cause of the pain. Are you missing an appendicitis or a DVT?
- Opiates can cause respiratory depression and even death. Patients on high doses should be on pulse oximeters and changes in respiratory rates and oxygen saturation should be taken seriously. Remember to set appropriate parameters for age.
- Most patients will require orders for relief of both chronic and breakthrough pain.
- Short-acting medications may be used initially, but once pain is controlled and the patient is on a stable regimen, long-acting medications should be ordered.
- The oral route is generally preferred, especially for patients who may be discharged to home or to another care setting. There are many pain control options available, although morphine is often a good initial choice.
- To maximize patient comfort, assess pain frequently and maintain a low threshold for changing dosage or agent if pain is not quickly and reliably controlled. Because patient needs often fluctuate, it is strongly recommended that physicians write orders for different pain levels (ie for mild pain give acetaminophen, for moderate pain give 1 mg Morphine, for severe pain give 3 mg morphine).
- Pain may be multi-faceted with varying etiologies and characteristics. After careful assessment, therapy should be tailored to the nature and cause of the pain. Multiple agents may be required to adequately control pain.
- **Naloxone (Narcan) dose for opioid intoxication:**
 - <20 kg: 0.1 mg/kg; repeat every 2-3 minutes if needed
 - ≥20 kg: 2 mg/dose; if no response, repeat every 2-3 minutes

Pain Assessment Protocol

Assess using a 0-10 scale. Patient should be asked: **“On a scale of 0-10 with ‘0’ being no pain and ‘10’ being the worst pain you can imagine, how much pain are you experiencing?”**

- If the pain is not a new symptom, it is important to ask the patient/family what usually works to relieve the pain and to initiate or continue this regimen.
 - If the patient cannot communicate, look for signs of discomfort such as grimacing, sweating, moaning, restlessness or guarding. Similarly, changes in vital signs (such as elevated respiratory rate) may be a sign that the patient is in pain.
 - If appropriate, consider asking family members how comfortable the patient appears as compared to baseline, and ask family members to keep the team apprised of changes in the patient’s apparent level of comfort.

Commonly used NSAIDs/Acetaminophen

(WE AVOID THESE IN ONCOLOGY PATIENTS BECAUSE THEY MASK FEVERS. Also, oncology patients should never receive NSAIDs as a general rule.)

NSAID	Dosage	Side Effects/Cautions
Acetaminophen	10 to 15 mg/kg/dose q 4 hr PO to a max of 650 mg/dose	May mask fever, hepatotoxicity at high doses
Ibuprofen	10 mg/kg/dose PO to a max single dose of 800 mg q 6 to 8 hr	May mask fever, avoid in patients with low platelets, may cause gastric irritation
Ketorolac (Toradol)	0.5 to 1 mg/kg as single dose IV to a max of 60 mg, followed by 0.5 mg/kg IV q 6 hr to a max single dose of 30 mg. PO: 0.25 mg/kg every 6 hours	May mask fever, avoid in patients with low platelets, may cause gastric irritation. Max duration is 5 days (useful in short term pain management).

Commonly used Opiates

Opiate	Dosage Form (UCSF formulary)	PO Starting Dose	IV Starting Dose	IV to PO conversion
Codeine	Tablet, as sulfate: 30 mg, 60 mg	0.5-1 mg/kg Q4-6hrs; max dose 60mg	N/A	N/A
Acetaminophen and Codeine	Elixir: Acetaminophen 120 mg and codeine phosphate 12 mg per 5 mL Tablet: Codeine/Acetaminophen 15/300mg (Tylenol #2); 30/300mg (Tylenol #3); 60/300mg (Tylenol #4)	0.5-1 mg/kg Q4-6hrs; max dose 2tablets/dose 15ml/dose	N/A	N/A
Acetaminophen and hydrocodone	Elixir: Hydrocodonebitartrate 2.5 mg and acetaminophen 167mg per 5ml Tablet: Hydrocodone/acetaminophen 5/500 mg; 7.5/500mg; 10/500mg	3-6yrs 5mL Q6-8hrs 7-12yrs : 10ml Q6-8hrs >12yrs: 1-2 tabs; max 8 tabs/day	N/A	N/A
Oxycodone	Capsule, immediate release (OxyIR®): 5 mg Liquid, oral: 5 mg/5 mL (500 mL) Solution, oral concentrate: 20 mg/mL (30 mL) Tablet: 5 mg Tablet, controlled release (OxyContin®): 10 mg, 20 mg, 40 mg, 80 mg	Instant release 0.05-0.15mg/ kg/dose Q4-6hrs; max 5mg/dose Controlled release (OxyContin®): 10mg Q12 (patients taking >20mg instant reloxycodone per day)	N/A	N/A
Morphine	IV Solution, oral: 10 mg/5 mL or 20 mg/5 mL OMS®, Roxanol®: 20 mg/mL Suppository, rectal (RMS®, Roxanol®): 5 mg, 10 mg, 20 mg, 30 mg Tablet: 15 mg, 30 mg Tablet: Soluble: 10 mg, 15 mg, 30 mg Sustained release (Oramorph SR™): 15 mg, 30 mg, 60 mg, 100 mg	0.3-0.6 mg/kg/dose Q12 for sustained release 0.2-0.5mg/kg/dose Q4-6hrs prn for solution (instant release)	0.1-0.2 mg/kg/dose Q2-4hrs; max dose 15mg/dose	10mg IV = 30-60 mg PO

Fentanyl	IV Lozenge, oral transmucosal: 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, 1600 mcg [raspberry flavor] Transdermal system: 12.5 mcg/hour 25 mcg/hour [10 cm ²]; 50 mcg/hour [20 cm ²]; 75 mcg/hour [30 cm ²]; 100 mcg/hour [40 cm ²]	Lozenge: <15kg contraindicated 15-40kg: 5-15mcg/kg; max dose 400mcg >40kg: 5mcg/kg max dose 400mcg	1-2mcg/kg/dose; max 50mcg/dose Continuous infusion 1mcg/kg/hr	N/A
Hydromorphone (Dilaudid®)	IV Suppository, rectal: 3 mg Tablet: 2 mg, 3 mg, 4 mg	0.03-0.08 mg/kg/dose PO Q4-6hrs; max 5mg/dose	15mcg/kg IV Q4-6hrs; max 2mg/dose	7.5mg PO = 1.5mg IV
Methadone	IV Oral (solution): 5 mg/5 mL; 10 mg/mL Tablet: 5 mg, 10 mg	0.1-0.2mg/kg/dose Q4-12hrs; max 10mg/dose	0.1mg/kg IV Q4-12 hrs; max 10mg/day	20mg PO = 10mg IV

Adjuvant Drugs

Category/Drug	Dosage	Indication	Comment
Amitriptyline (Elavil®) Antidepressant	0.2-0.5 mg/kg PO QHS Titrate upward by 0.25mg/kg weekly as needed; max dose 2mg/kg; usual starting dose 10-25mg Dosage forms: 10mg, 25mg, 50mg, 75mg, 100mg, 150mg	Continuous neuropathic pain with burning, aching, dyesthesia or insomnia	<ul style="list-style-type: none"> ◆ Provides analgesia by blocking re-uptake of serotonin and norpinephrine ◆ Good for pain related to insomnia or depression ◆ Analgesia takes effect before antidepressant ◆ Side effects dry mouth, constipation, urinary retention, and black box warning regarding increased risk of suicide in children
Gabapentin (Neurontin®) Anticonvulsant	5mg/kg PO at bedtime increase to BID on day 2, TID on day 3 Max:300 mg/day Dosage forms: 100mg, 300mg, 400mg	Excellent neuropathic pain blocker	<ul style="list-style-type: none"> ◆ Major side effect is sedation but can cause ataxia, nystagmus, dizziness
Lorazepam (Ativan®) Anxiolytic	0.03-0.1 mg/kg Q4-6hrs PO/IV; Max 2mg/dose	Anxiolytic	<ul style="list-style-type: none"> ◆ May increase sedation, not effective as an analgesic but provides excellent anxiolysis
Diazepam (Valium®) Anxiolytic	0.1-0.3 mg/kg Q4-6hr PO/IV; Max 10mg/dose	Anxiolytic	<ul style="list-style-type: none"> ◆ May increase sedation ◆ Longer onset of action than lorazepam

Dexamethasone Steroid/Anti-inflammatory Agent	Dose dependent on clinical situation; high bolus dose in cord compression Cerebral Edema: 1-2 mg/kg load then 1-1.5mg/kg/day divided Q6hrs; max 4mg/dose Anti-inflammatory: 0.08-0.3 mg/kg/day divided Q6-12 hrs	Increased intracranial pressure, bony metastasis, cord compression	◆ Steroid side effects- gastric irritation (use gastroprotectant), edema, weight gain, acne
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Useful Opiate Information

Opioid Analgesic	Onset (min)	Peak (hours)	t _{1/2} (hours)	Equianalgesic Dose (milligrams)	
				Oral	Parenteral
Morphine	15-60	0.5-1	1.5-2	30	10
Hydromorphone (Dilaudid®)	15-30	0.5-1	2-3	7.5	1.5
Oxycodone	15-30	1		20	-----
Methadone	30-60	0.5-1	15-30	20 acute 2-4 chronic	10 acute 2-4 chronic
Fentanyl	7-8	Early	1.5-6	-----	0.1

Maintenance of a Continuous Intravenous Infusion

The initial maintenance dose is based on a rough estimate of the elimination half-life of the opioid. For morphine and hydromorphone, the elimination half-life averages 3 hours. The initial maintenance dose can be calculated using the following formula:

$$\text{Estimated hourly maintenance dose} = \frac{\text{Loading dose}}{(\text{Elimination half-life, in hrs.}) \times 2}$$

For example, if the patient requires morphine 10 mg IV x 3 to achieve initial pain control, the estimated hourly maintenance dose is $30/(3 \times 2) = 5$ mg qhour, order morphine 5-10 mg IV q2h. For patients without an IV, SQ administration is a good choice – the doses are equal to those for IV. Assess the patient frequently and adjust the dose to achieve an appropriate balance of pain control and level of sedation.

Pharmacologic Management of Opiate Side Effects:

Side Effect	Pharmacologic Intervention
Pruritus	<p>Diphenhydramine (Benadryl®): 1 mg/kg IV/PO Q4-6hrs; max 25 mg/dose</p> <p>Hydroxyzine (Atarax®): 0.6 mg/kg/dose PO Q6hr; max 50 mg/dose</p> <p>Naloxone: 0.5 mcg/kg/hr continuous infusion (diluted in a solution of 0.1 mg of naloxone per 10ml of saline)</p>
Sedation	<p>Caffeine: single dose of 2.5-5 mg PO (may also consider caffeinated drinks)</p> <p>Dextroamphetamine (Adderall®): 2.5-5 mg PO in AM and early afternoon</p> <p>Methylphenidate (Ritalin®): 2.5-5 mg PO in AM and early afternoon</p>
Confusion/hallucinations	<p>Eliminate adjuvant meds with CNS effects (such as benzodiazepines)</p> <p>Consider opiate switch</p>
Constipation	<p>Senna and docusate sodium (Colace): 2-6 years: ½ tab qday; advance to max 1 tab BID 6-12 years: 1 tab qday; advance to max 2 tabs BID >12 years: 2 tabs qday; advance to 4 tabs BID</p> <p>Bisacodyl (Ducolax): PO or PR 3-12 years: 5 mg/dose/day >12 years: 10-15 mg/dose/day</p> <p>Lactulose: 7.5 mL/day after breakfast; adults 15-30 mL PO qday</p> <p>Magnesium citrate: < 6 years: 2-4ml/kg PO x 1 6 - 12 years: 150-300 mL PO x 1</p> <p>Polyethylene glycol (Miralax®) <10 kg: ½ capful (8.5g) PO qday-TID >10 kg: 1 capful (17g) PO qday-TID</p>

Respiratory depression	<p>Mild-Moderate: Hold opiate and reduce subsequent doses by 25%</p> <p>Severe: Naloxone: Birth (including premature infants) to 5 years or < 20 kg: Initial: 0.1 mg/kg (maximum dose: 2 mg)</p> <p>> 5 years or ≥ 20 kg: 2 mg/dose; if no response, repeat every 2-3 minutes</p> <p>During sedation for procedures: 5-10 mcg/kg until breathing improves</p> <p>Hold further opiates; reduce subsequent dosing if possible</p>
Nausea/Vomiting	See anti-emetic section
Urinary retention	<p>Eliminate adjuvant drugs (e.g. antihistamines, tricyclics); consider indwelling foley catheter</p> <p>Oxybutynin: 1 year 1mg TID 1-2 years 2mg TID 2-3 years 3mg TID 4-5 years 4mg TID >5 years 5mg TID</p>

References:

UCSF formulary & Lexi-Comp

Many figures were adapted from “Pain Management in Children with Cancer” by Hockenberry-Eaton M *et al.* at Texas Children’s Hospital in Houston, Texas:

www.childcancerpain.org

PALLIATIVE CARE

Palliative care is a philosophy of care that focuses on quality of life and relief of symptoms for patients with life-threatening illness. This includes attention to emotional, psychosocial, and spiritual issues for patients and family members. Palliative care is not limited to end of life care and may often occur in conjunction with curative or life-prolonging care. Goals of palliative care:

- To prevent/relieve physical, psychosocial and spiritual suffering.
- To achieve the best possible quality of living and dying for patients and their families.
- To enhance and maximize the family's strengths and capacity to cope.
- To anticipate and prepare the child and family for expected/potential changes in their lives.
- To provide care that is sensitive to personal, cultural and religious/spiritual values, beliefs and practices

Compass Care Services

Compass Care program provides comprehensive palliative care for children who require end-of-life care, as well as children with chronic life-threatening conditions who may live for many years or eventually be cured. Compass Care is available 24 hours a day by page 443.4248.

- Care focusing on quality of life and relief of suffering. This includes pain and symptom management and, if necessary, end-of-life care.
- Child and family support
- Child and family education
- Staff education on palliative care
- Comfort Care Spaces in the pediatric unit designed to provide a private, home-like atmosphere for end-of-life care.
- Comfort Care Cart for the pediatric unit. The cart is stocked with blankets, journals, snacks, neck pillows, books and other items that provide an extra measure of comfort for end-of-life care.
- Meeting families' spiritual, religious, and cultural requests
- Family portraits for terminally ill children
- Family bereavement services, such as an annual memorial event
- Sibling services, such as Sibling Awareness Week
- Family resource library
- Family Support Program
- Assistance in identifying community home care or hospice resources

Psychosocial Care Services

A chaplain is available 24 hours a day by pager 443.2273.

- Offer spiritual and emotional support.
- Pray with children/families.
- Conduct or arrange for religious/spiritual rituals.
- Join with children/families in reading scripture or other spiritual literature.
- Arrange for visits by clergy of any faith.

Child Life Services

Families dealing with life threatening illness often have questions and concerns regarding the patient's and/or sibling's developmental understanding of death and dying. Child life specialists and teachers work closely with the medical team to provide the best possible care for each child and family. Child life specialists and teachers work with children and families individually to ensure that their developmental, emotional and psychological needs are being met. They can be reached at 353.1203 or by pager 443.4914.

- Emotional support for the child, including non-pharmacological pain management, end-of-life wishes, and good-byes.
- Sibling support, including education about the situation, expressive opportunities, and saying good-bye.
- Parental support and education regarding how to talk with the ill child, siblings, extended family, and friends.
- Creation of keepsakes (handprints, memory boxes, photos, etc.).

Social Work Services: See social work section of manual

Monitoring Vital Signs

Vital sign monitoring for patients who are imminently dying should be minimized and used only to promote comfort. For example, temperature may be monitored if fever is causing uncomfortable symptoms. Vital sign monitoring for patients who are not imminently dying should be guided by the treatment goals.

SYMPTOM	Monitoring For Patients Who Are Imminently Dying	Monitoring For Patients Who Are Not Imminently Dying
Pain	A common symptom. Should be assessed frequently and treated aggressively.	A common symptom. Should be assessed frequently and treated aggressively.
Dyspnea	A common symptom. Should be assessed frequently and treated aggressively.	A common symptom. Should be assessed frequently and treated aggressively.
Anxiety/agitation	A common symptom. Should be assessed frequently and treated aggressively.	A common symptom. Should be assessed frequently and treated aggressively.
RR	An important sign of possible distress	Monitor q shift
HR	May not be indicated	Monitor q shift
BP	May not be indicated	Monitor q shift
Temperature	May not be indicated	Monitor q shift
O2 Saturation	May not be indicated	Monitor q shift

Symptom	Monitoring For Patients Who Are Imminently Dying	Monitoring For Patients Who Are Not Imminently Dying
Pain	A common symptom. Should be assessed frequently and treated aggressively.	A common symptom. Should be assessed frequently and treated aggressively.
Dyspnea	A common symptom. Should be assessed frequently and treated aggressively.	A common symptom. Should be assessed frequently and treated aggressively.
Anxiety/agitation	A common symptom. Should be assessed frequently and treated aggressively.	A common symptom. Should be assessed frequently and treated aggressively.
RR	An important sign of possible distress	Monitor q shift
HR	May not be indicated	Monitor q shift
BP	May not be indicated	Monitor q shift
Temperature	May not be indicated	Monitor q shift
O2 Saturation	May not be indicated	Monitor q shift

Fever

Assess for discomfort and if indicated, treat aggressively with the following:

- Tylenol and/or ibuprofen.
- Sponge bath or sitz bath with tepid water to reduce fever quickly.
- Dress lightly; provide for privacy and dignity.

Pain Control

Most patients will require orders for relief of both chronic and breakthrough pain. Short-acting medications may be used initially, but once pain is controlled and the patient is on a stable regimen, long-acting medications should be ordered. The oral route is generally preferred, especially for patients who may be discharged to home or to another care setting. Although there are many pain control options available, morphine is often a good initial choice. To maximize patient comfort, assess pain frequently and maintain a low threshold for changing dosage or agent if pain is not quickly and reliably controlled. Because patient needs often fluctuate, it is strongly recommended that physicians write for a dosage range when prescribing opioid analgesics. See *Pain Control Section of manual for additional information.*

Seizures

Phenobarbital

Phenytoin

Diazepam (can give IV formulation PR)

Lorazepam

Clonazepam (Klonopin®)

Dyspnea

Some dyspnea is not associated with hypoxia and not all hypoxia manifests as dyspnea; a work-up may be indicated. Dyspnea should be assessed using a 0-10 scale. Patient should be asked if able to respond, “On a scale of 0-10 with ‘0’ being no shortness of breath and ‘10’ being the worst shortness of breath you can imagine, how short of breath are you now?” If patient cannot communicate, respiratory rate may also be monitored as a surrogate indicator. If appropriate, consider asking family members how short of breath the patient is compared to baseline, and ask family members to keep the team apprised of changes. Oxygen therapy is often an appropriate treatment, especially if the patient is hypoxic. A mask may be too constricting and can actually worsen dyspnea. If the dyspnea is not a new symptom, it is important to ask the patient/family what usually works and to initiate or continue this regimen. If the dyspnea is a new symptom and the patient wishes, consider a work-up to identify and treat the underlying cause of the symptom. Additional management strategies include:

- Ask the child/family what works best to promote comfort.
- Assess for most comfortable position.
- Dress the child in loose fitting clothes.
- Raise head of bed at least 30-45 degrees and position child with pillow.
- Use fan to circulate humidified air (directed towards child).
- Assess and treat for excessive secretions.
- Decrease IV fluid intake; in the terminal phase consider discontinuing IV fluids.
- Consider PRBC transfusion for comfort.
- Nebulized bronchodilators may provide symptomatic relief of dyspnea in certain circumstances.
- Use of a diuretic may be helpful for pulmonary edema.
- Around the clock opioid medication dosing recommended.
- Treat anxiety.
- Use behavioral strategies (guided imagery, relaxation, music tapes, breathing exercises) to help mitigate symptoms.

Anxiety

- Consider physical, emotional, spiritual, and cultural influences; often multifactorial
- Rule out opioid toxicity; adjust medications accordingly.
- Child will respond to family’s anxiety, so remember to take care of their needs as well as the child’s.
- Sit with child/family to listen, teach, support and guide them through the process.
- Consider music, soft lighting, quiet environment, and guided imagery.
- Assess for depression and treat accordingly.
- Involve Child Life, Social Work and Spiritual Care as appropriate: nonpharmacologic treatment can include supportive psychotherapy, relaxation therapy, guided imagery, and hypnosis.
- *Pharmacological Treatment:*
 - First line benzodiazepines in patients with terminal illness: lorazepam and oxazepam are the safest in hepatic disease and are the shortest-acting.
 - Diazepam may be useful if a long-acting agent is desired.
 - Neuroleptics are indicated if anxiety is associated with psychosis

Secretions

- Consider decreasing or stopping IV fluids if appropriate to goals.
- If child has lung disease, consider stopping IV fluids sooner to prevent secretion accumulation.
- Reposition child judiciously every 2 to 4 hours.
- Raise head of bed at least 30-45 degrees and position child with pillow.
- Consider gentle superficial suction with a soft catheter. Avoid deep suctioning.
- Medication choices include glycopyrrolate (Robinul®), scopolamine, and Levsin

Constipation

- Evaluation to include history, medication review, abdominal exam to exclude ileus, intestinal obstruction or fecal impaction.
- Prophylaxis is best approach, so start bowel regimen all patients on opioids; prescribe bowel stimulant + softener.
- Schedule regular doses and titrate dose to response or side effects; aim is regular, comfortable BMs.
- Privacy is also an important factor to be considered.
- Liquid stool can be a symptom of impaction; take a good bowel history.
- Treatment choices: prune juice, docusate, Miralax, bisacodyl, senna, and milk of magnesia.

Diarrhea

- Laxatives are the most common cause of diarrhea in palliative medicine. Fecal impaction can also present as diarrhea (encopresis).
- Evaluation should include history, medication review (antacids, antibiotics, iron, NSAIDs, etc.), abdominal exam and stool cultures if indicated.
- If unable to treat specific cause of diarrhea treat generally with anti-diarrheals.
- Loperamide is preferred because it is more effective and has fewer systemic side effects than other anti-diarrheals.

Nausea and Vomiting

- Treatment should be based on identifying etiology, emetogenic pathway, and associated neurotransmitter.
- Choose most potent antagonist, select appropriate route of administration, dose around the clock, titrate carefully and reassess frequently.
- If no response, then reevaluate and consider alternative agent or route of administration.

Treatment options:

Pharmacological

Drug Class	Name	Indication
5-HT ₃ -receptor antagonist	ondansetron, granisetron	Acute and delayed chemotherapy-induced nausea and vomiting
Corticosteroid	dexamethasone	Acute and delayed chemotherapy-induced nausea and vomiting Partial intestinal obstruction Hepatic capsular distension Raised intracranial pressure
NK ₁ -receptor antagonist	aprepitant	Acute and delayed chemotherapy-induced nausea and vomiting
Anti-Histamine	diphenhydramine	Enhanced vestibular sensitivity
Anti-Cholinergic	Scopolamine	Enhanced vestibular sensitivity
Prokinetic	metoclopramide	Dysmotility Delayed gastric emptying Drug-induced
Buterophenomes	haloperidol	General purpose
Cannabinoid	dronabinol	Acute and delayed chemotherapy-induced nausea and vomiting

Non-Pharmacological

- Wear loose-fitting clothing.
- Eat small frequent meals. (If any of your patients prefer not to eat or drink in order to manage nausea and vomiting, recognize and respect their decision.)
- Maintain a relaxed atmosphere.
- Try complementary therapies (e.g., diversion, relaxation, hypnosis, guided imagery, and acupuncture).

Insomnia

Evaluation: identify and characterize complaint; document sleep-wake cycle; identify precipitants; consider individual sleep requirements; review medication, neuropsychologic and substance use history; physical examination; review lab data.

Treatment includes sleep hygiene, environmental modification, and medication. Consider short-acting benzodiazepine if difficult to initiate sleep (lorazepam). Alternatives include sedating antidepressants like amitriptyline (anticholinergic), trazodone (less anticholinergic), diphenhydramine (anti-histamine), and zolpidem (non-benzodiazepine hypnotic).

Terminal Restlessness

- Can occur near the time of death, usually within 72 hours.
- Prepare family for this potential symptom.
- Treat pain and anxiety first.
- Provide emotional and spiritual support for child and family.

GUIDELINES FOR DECLOTTING CENTRAL VENOUS CATHETERS (CVCS) WITH ALTEPLASE [TISSUE PLASMINOGEN ACTIVATOR (TPA)]

SUMMARY

Thrombotic occlusion is a common complication of CVC. This can lead to the interruption of administration of intravenous medications, fluids, and blood products as well as prevent blood sampling. An associated increased risk of bacterial line infections has also been reported. Efforts should be made to exclude other mechanical mechanisms of occlusion (e.g. positioning, medication concretions). When catheter occlusion occurs, two options are considered: restoring patency or replacing the catheter. Thrombolytic agents are used to restore catheter patency in an attempt to salvage the catheter and avoid the risks and expense associated with catheter replacement. Alteplase [tissue plasminogen activator, (tPA)] has become the drug of choice in catheter clearance in children. While it is quite expensive, studies assessing the efficacy of Alteplase use to restore CVC patency in infants and children demonstrated 85-95% success rates. Further, the intraluminal (dwell and withdrawal) administration of tPA is safe, with only rare case reports of complications.

NOTE: this is NOT the management of a CVC-associated thrombus.

There are two methods of alteplase administration for treating occluded central venous catheters:

- 1) Intraluminal: administration of low dose alteplase into the catheter lumen.
- 2) Infusion systemic administration of alteplase by slow infusion.

INDICATIONS

Intraluminal administration:

- 1) Confirmed complete catheter occlusion, i.e.; the inability to flush or aspirate blood.
- 2) Partial occlusion or withdrawal occlusion, i.e., the catheter flushes but it is not possible to aspirate blood.
- 3) Sluggish action of catheter flushing or withdrawal of blood.

Systemic administration by infusion:

- 1) Confirmed withdrawal occlusion caused by fibrin that has failed intraluminal Alteplase administration.
- 2) Venography verification of fibrin sheath.

CONTRAINDICATIONS

- 1) Active bleeding, history of bleeding.
- 2) Recent trauma.
- 3) Recent intracranial or intraspinal surgery or trauma.
- 4) Intracranial hemorrhage.
- 5) Familial or acquired bleeding diatheses.
- 6) Neurosurgery within the last two months.
- 7) History of stroke or intracranial metastasis.
- 8) Hypersensitivity to the thrombolytic agent.
- 9) Major surgery or lumbar puncture.

- 10) Thoracentesis or paracentesis within the last four days.
- 11) Any abnormal coagulation studies (PT, PTT, fibrinogen, platelets).
- 12) A history of heparin induced thrombocytopenia
- 13) Intracranial neoplasm, arteriovenous malformation or aneurysm.
- 14) Severe uncontrolled hypertension.
- 15) Acute ischemic stroke.

INTRALUMINAL ADMINISTRATION (Low dose)

Precautions

The most common adverse event associated with alteplase use is bleeding.

In patients at risk of low fibrinogen levels (e.g., s/p multiple asparaginase doses or DIC), consider checking the fibrinogen level prior to administration of each dose of alteplase. If the fibrinogen is low, consider administration of FFP to correct prior to alteplase administration.

Precautions should be taken to prevent the administration of systemic alteplase (i.e., flushing the dose out of the catheter into systemic circulation). If it is possible that the patient received > 0.05 mg/kg of alteplase systemically, consider checking fibrinogen level and monitor the patient for evidence of bleeding.

Dosage

- The optimal dose and solution volume depends on the internal volume of the catheter. UCSF nursing policy is to infuse the volume of the catheter (the medication safety RNs have a chart with catheter type, French, and internal volume for reference). For port-a-caths, use 2 mL of alteplase.
- While both lumens of a multi-lumen catheter may need to be treated for partial withdrawal occlusion, each lumen should be treated one at a time.
- The concentration used is 1 mg/mL for infants and children > 10 kg
- The concentration used is 0.5 mg/mL for neonates and infants < 10 kg
- Alteplase should not be used in preterm neonates.

Preparation

- Pharmacy will prepare 1mg/ml, 2ml syringes.
- For the 0.5 mg/mL (neonatal/infant) concentration – dilute 1 mL of 1 mg/mL concentration with 1 mL of sterile water for injection or preservative free 0.9% NaCl at the time of administration.

Administration

- Instill alteplase (volume depends on individual catheter volume) into the venous access device. Allow to dwell for 30 – 120 minutes.
- After dwell time attempt to aspirate the contents from the venous access device.
 - if aspiration is successful, flush the device with an appropriate volume of normal saline.
 - if aspiration is difficult and not complete, consider a 2nd dose.

- if aspiration is not successful, attempt to aspirate the alteplase injected into the device. If aspiration is successful, administer a second dose. If aspiration is not successful, wait 8-12 hours and attempt to aspirate the contents again. Repeat the dose if needed.

- If the local administration procedure is not effective in clearing the catheter occlusion, consider the systemic administration of alteplase.

Sample Orders

“Please instill 2 mL of 2 mg/2 mL t-PA solution into occluded port-a-cath. Let dwell for 30-120 minutes before aspirating. If not able to aspirate, may repeat dose x 1.”

“Please instill 0.8 mL of 2 mg/2 mL t-PA solution into occluded 7 French Broviac. Let dwell for 30-120 minutes before aspirating. If not able to aspirate, may repeat dose x 1.”

SYSTEMIC ADMINISTRATION BY INFUSION

NOTE: Systemic administration of t-PA should not be performed without the knowledge of the attending physician.

Precautions

See above contraindications. Patient should be assigned strict bed rest during the infusion.

Monitoring:

Pre-Infusion

- Obtain: CBC, PT, PTT, Platelet , Fibrinogen
For hemodialysis patients, wait 6 hours after completing the dialysis procedure to minimize the heparin effect on the coagulation profile.

During Infusion

- Obtain Fibrinogen level after 4 hours of infusion.
 - A fibrinogen of < 100 indicates a bleeding risk – assess risk / benefit.
 - If fibrinogen is <100 but > 50, consider decreasing the dose, closely monitor for evidence of bleeding and pain, and monitor vital signs every 2 hours.
 - If fibrinogen < 50 - Stop infusion.
- Monitor for signs of bleeding.

Dosage

- The systemic dose is 0.1 mg/kg/h for 6 hours with a maximum dose of 50 mg.
- The dose is the same if clearing a single or multi-lumen catheter.
- If the first infusion is not successful, wait 12-24 hours and reevaluate the fibrinogen level. Document a normal fibrinogen level before initiating a repeat dose. Once the fibrinogen level has recovered, consider a second infusion of 0.1 mg/kg/h for 6 hours. Maximum dose is 50mg.
- The dose is the same for neonates, infants, and children. Alteplase should not be used in preterm neonates.

Preparation

Alteplase is supplied in a ready-to-mix kit. This kit contains a 50 mg vial of alteplase and a 50 mL vial of sterile water for injection. Alteplase has an eight-hour stability once reconstituted. Immediately before use, the alteplase should be reconstituted with the 50ml of sterile water for injection to yield a 1 mg/mL concentration. Strict aseptic technique is essential.

Administration

The reconstituted 50 mL of 1mg/mL alteplase should be drawn into a syringe and administered via syringe pump or other appropriate controlled infusion device. Systemic Alteplase should be administered via a peripheral IV or short (to mid-upper arm) PICC in the hand or arm. If peripheral IV access is not available, the distal port of the catheter may be used.

MD INSTRUCTIONS FOR PATIENT HLA TYPING

1. ***Before*** sending blood for HLA typing, ensure there is insurance approval (usually obtained by Hilda de la Cruz; 353.4482).
2. Complete “HLA Typing Requisition” found in folder in residents’ work room; instructions on inside of folder – please fill out “yellow highlighted” areas found on sample req. – MD should fill this out. *Please note – there are two sets of instructions – one for “MUD recipient typing” and one for “related donor and recipient typing”*
3. Put the requisition in a lab bag and tape to the inside cover of the patient’s chart.
4. Write the MD ORDER as follows: *“Please send one full yellow ACD tube for HLA typing to 5th floor lab with morning labs - requisition is in the front of the patient’s chart.”*

PLEASE NOTE: IF HLA typing is needed for a family member, the requisition needs to be completed and given to the family member to have the blood drawn at the outpatient lab across the street. PLEASE ensure insurance approval is obtained prior to the blood draw.