ONCOLOGY HANDBOOK
for trainees on the PHO inpatient service
prepared by L Stork MD (revised 6-28-10)

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ONCOLOGY EMERGENCIES

I. FEVER AND NEUTROPENIA (F and N) S/P myelosuppressive chemotherapy

Neutropenia = ANC < 500/mcl (ANC = WBC/mcl x [% segs + bands])
Fever = T > 101°F (38.3°C), taken by any route, or T > 100°F (38°C) [< 101 °F]
repeatedly in a 24 hours period.

(APC = WBC/mcl x [%segs + bands + monos])

Rationale for Broad Spectrum "Emergency" Antibiotics:

1) Signs of infection altered (especially if ANC < 100/mcl): decreased exudate,
   fluctuance, necrosis, drainage, swelling, dysuria, consolidation (pneumonia).
   Erythema and pain, although diminished, are often present.

2) High morbidity/mortality: approximately 50% of neutropenic patients with untreated
   gram-negative bacteremia die within 48 to 72 hours.

Pertinent History:

1) Dates of last chemotherapy and type of chemotherapy (most ANC nadirs occur
   between days 7 - 14 post chemo and last three to five days before signs of myeloid
   recovery appear). The degree and duration of neutropenia directly correlate with the
   risk of infection.

2) Previous documented infections

3) Presence of central line (single or double lumen).

4) Previous splenectomy

5) Infectious disease exposure

6) Symptoms: cough, dyspnea, chest pain, retrosternal pain, sore throat, dysphagia,
   heart burn, abdominal pain, pain with defecation, vomiting, diarrhea, skin sores.

Physical Exam:

Special attention to: vital signs; TM; oral mucosa; oral pharynx; lungs (tachypnea,
grunting, flaring, retractions, hypoxia); perirectal area, (visual inspection and pain
assessment with external pressure but no routine rectal exam while neutropenic); skin
(erythema, vesicles, pustules, ecthyma gangrenosum); catheter exit site or
subcutaneous port site and catheter tract; sites of previous bone marrow aspirates or
spinal taps, venipunctures, finger sticks.
Diagnostic Evaluation:

Cultures:

Blood cultures: One blood culture from each lumen of a central venous catheter is initially required. Peripheral cultures ("arm poke") are not required unless the patient has no central line, in which case one peripheral blood culture should be obtained.

Urinalysis and urine culture (do not wait for sample before starting antibiotics).

Areas of localized signs of infection require appropriate procedure for culture. Oral mucosal lesions or perirectal lesions may be cultured for herpes simplex, aerobes, anaerobes, fungus.

Radiographs: Routine chest x-rays are not indicated unless a pulmonary sign or symptom is present or fever persists beyond 48 hours.

Treatment: Intestinal tract, skin, and respiratory tract (lungs and sinuses) are the likely sources of microorganisms

1) Broad spectrum antibacterial antibiotics:
   a) Ceftazidime (Fortaz) 150 mg/kg/day ÷ q 8 hours (50 mg/kg/dose – max 2 g/dose) covers essentially all gram-negative organisms including pseudomonas, many gram-positive organisms except for coag negative staph, alpha strep (non-pneumococcal), enterococci, and is intermediate for staph aureus. To be started on all patients (unless allergic) ASAP (even before patient is examined by M.D., if necessary). (Cefipime may replace ceftazidime for empiric antibiotics treatment of F & N in high risk patients).

   b) Vancomycin 40 mg/kg/day ÷ q 6-8 hours (adult max usually 2 gm/day ÷ q 12h) covers all gram-positive organisms (aerobes and anaerobes) including coag - staph, staph aureus, alpha strep, enterococci, and clostridium perfringens; except vanco-resistant enterococcus (VRE). Trough levels need to be followed if the patient has impaired renal function, will be on it >3 days, or has persistent fevers. Vancomycin should be started on the following patients ASAP:

   1) all patients whose preceding chemotherapy course included high dose cytarabine (1-3 g/m²) (high incidence of α-strep bacteremia)
   2) signs of septic shock are present
   3) signs of infection around catheter exit site, SQ port site, or along catheter tract
   4) previous history of coag negative staph with the same central line, alpha strep or enterococcal bacteremia.

2) Hydration:
   Hydration with either D51/2 NS (at least maintenance rate) or NS (see shock below) should begin as soon as possible after the patient is evaluated in the ED or inpatient unit, regardless of fluid or circulatory status. Patients with bacteremia (especially with gram – rods) but clinically stable may suddenly develop signs of endotoxic shock during or after the antibiotic is infused. Unless a patient with fever and neutropenia looks quite well, an initial bolus of 10 ml/kg x ½ -1 hour should be given at the time of
initiation of antibiotics. This rate and subsequent fluid should be adjusted to the
clinical course (see shock below).

3) Candida albicans prophylaxis:
Prevention of oral candidiasis (thrush) should be considered if the patient is on
antibiotics > 3 days and is receiving steroids as part of the cancer treatment
regimen: oral Mycostatin (5-10 cc BID swish and swallow), Clotrimazole troches (1,
suck x 20 minutes and swallow BID), or fluconazole (3 – 6 mg/kg/day p.o. or IV).
Avoid fluconazole in ALL Induction – interferes with Vincristine, Daunomycin, or
Doxorubin metabolism by inhibiting Cyp3/4A system.

4) Anti-pyretics (for T>101°F [38.3°C] ) : Acetominophen (15 mg/kg) q 4 hour p.o. (no
routine rectal meds*) and/or Ibuprofen (10 mg/kg) every 6 hours. The latter drug
should be given with caution if platelets < 50K or symptoms of gastritis present.
  * An occasional patient may benefit from rectal Acetominophen, which is
    relatively safe for a patient already receiving antibiotics.

5) Indications for anaerobic bacterial coverage in patients with F and N:
Treatment with IV Clindamycin or IV Metronidazole (Flagyl) [or Meropenem in lieu of
ceftazidime] may initially be indicated if the physical exam or x-rays reveal:
  a) perirectal pain or erythema
  b) abdominal pain and possible typhlitis,
  c) severe or recurrent sinusitis,
  d) severe oral/esophageal mucositis

4) F and N with clinical signs of septic shock: often warm shock with borderline BP

Aggressive fluid resuscitation (up to 60 cc/kg x 1 h) is more important than
antibiotics. Initial treatment should include Ceftazidime, Vancomycin, and an
Aminoglycoside, like Tobramycin. Continue fluid resuscitation with crystalloid or
colloid (blood products or albumin) until impending pulmonary edema. Dopamine for
vascular support and ICU admission may be necessary.

Duration of Antibiotic Treatment:

1) Documented bacteremia: treat for 10 to 14 days with appropriate antibiotics, or until
ANC > 500, if longer. Document negative blood culture before stopping treatment..

2) Culture proven source: treat for duration recommended for source in normal host, or
until ANC > 500 if longer.

3) No documented source: treat at least 48 hours with IV broad-spectrum antibiotics.
In all likelihood, a patient S/P F & N without documented source of infection (and no
URI symptoms) had a "nidus" of bacteria stimulating fever that was "nipped in the
bud" with antibiotics. Criteria for discontinuing antibiotics and discharging to home
regardless of ANC include:

1) Admission cultures remain – after 48 hours and no source on exam, and
2) Minimum of 24 hours afebrile and looking well prior to d/c, and
3) Parents of patients discharged with ANC < 500 should be advised to notify oncology service, as usual, for T>101°F [38.3°C].
4) Some evidence of recovering marrow, including rising monocyte count or plt count with ANC > 100
5) For patients on G-CSF, evidence of rising ANC (or APC = WBC x % [segs + bands + monos] is usually required, which generally reaches > 500 rapidly

The majority of patients with F and N become afebrile within the first 36 hours of admission on antibiotics. If fever persists beyond 48 hours, one should consider additional antibiotic coverage (i.e. Vancomycin, anaerobic coverage, Acyclovir). The patient should be re-evaluated for a source of infection (thorough physical exam, chest x-ray, sinus films, etc.)

II. SPECIAL INFECTIOUS PROBLEMS:

A) Pulmonary symptomatology present on exam:

Immunocompromised patients are predisposed to pulmonary infections with CMV and other viruses, mycoplasma, Pneumocystis carinii, legionella, and fungus, whether or not they are neutropenic. The majority of patients on chemo receive prophylactic TMP/SMZ throughout treatment (2.5 mg/kg/dose TMP equiv BID each Sat/Sun). Chest x-ray and pulse-oximetry should be obtained in any patient with tachypnea or auscultatory findings on exam. Nasal wash for all viruses should be obtained. CMV PCR of blood should be considered. An O2 requirement is an indication for chest CT scan, pulmonary consultation and broncho-alveolar lavage (BAL). Empiric treatment with Azithromycin, and TMP/SMZ (depending on compliance history) should be considered (along with Ceftazidime +/- Vancomycin if neutropenic) while awaiting work-up results. Chest CT is much more likely to identify pulmonary nodules than CXR. Subsequent interventional radiology aspiration of a pulmonary nodule or open lung biopsy may be required for precise diagnosis. Antifungal treatment should be empirically begun if nodules are seen on CT whether or not biopsy is planned.

B) Rule out typhlitis:

Typhlitis is similar to NEC in newborns. It is an inflammatory cellulitis of the intestines, particularly the cecum. It occurs primarily in patients with ALL and AML during the first several weeks following diagnosis. These patients are usually neutropenic, anemic, and thrombocytopenic at the time of presentation with typhlitis. Abdominal signs may be subtle in these patients because of neutropenia and because Prednisone or Dexamethasone (treatment for ALL) further masks signs of inflammation. Mild abdominal pain in these patients should be aggressively evaluated and managed, with serial abdominal exams and serial abdominal films to evaluate bowel wall thickening, mucosal edema, pneumatosis intestinalis, or free air. CT scan of the abdomen is usually helpful in defining typhlitis. Serial blood cultures and serum HCO₃ should be obtained. Surgical consult should be obtained at the time typhlitis enters the differential. Patient should be NPO. Antibiotics should include gram-positive, gram-negative and anaerobic coverage. Emergency surgery may be indicated to remove infarcted or perforated bowel.
Differential diagnosis of abdominal pain during ALL Induction:
1. constipation/obstipation (ileus from Vincristine)
2. gastritis/ulcer (from steroids + stress)
3. pancreatitis (from PEG Asparaginase)
   (median time from Peg Asp injection until clinical pancreatitis is 10 days)
4. c.difficile enterocolitis (S/P antibiotics)
5. typhlitis

C) Possible central line infection with fever without neutropenia.

Oncology patients are at risk for central line infections even when not neutropenic. The decision whether or not to empirically treat pending culture results (despite ANC > 500) requires thoughtful clinical judgment. Obvious signs of infection related to the catheter require early treatment after blood cultures are drawn. A significantly higher than normal WBC and/or band count for the particular patient should raise suspicions of line infection. (Bandemia is common [up to about 20%] as bone marrow recovery follows chemotherapy, but is usually associated with monocytosis and ANC < 1000.) Ceftriaxone IV q day as outpatient is generally inadequate empiric treatment of presumed line infection, as coag - staph and pseudomonas are resistant to that drug.

Coag negative staph catheter infection may require treatment x 14-21 days, as coag negative staph makes “slime” that sticks to catheters. After full treatment, a vancomycin lock q 24 hours x 7-14 days, which allows the catheter lumen to “bathe in vanco”, may be beneficial for recurrent staph epi infections and prevent or forestall the need for line removal.

D) Criteria for central venous catheter removal: (with or without neutropenia)

1) septic shock not responsive to fluid and pressors
2) persistent bacteremia after about 48 hours of appropriate antibiotic treatment
3) prolonged fever with a documented line infection
4) bacterial endocarditis
5) tunnel infection (along catheter tract) or cellulitis around infusaport
6) fungemia/candidemia
7) certain specific organisms, like enterococcus and candida

E) Clostridium difficile enterocolitis:

This is not uncommon in the oncology population. Any oncology patient who develops diarrhea (with or without blood) should have stool tested for c. difficile toxin and, depending on clinical suspicion, for enteric bacterial pathogens and viruses as well (parasites are uncommon in this population, except for Giardia). If there is a high index of suspicion for c. difficile, or the patient has significant GI symptoms, like crampy abdominal pain, empiric treatment with oral Metronidazole (Flagyl 30 mg/kg/day divided TID, maximum 1 gram/day) may be started while waiting for test results. Full treatment is for 7-10 days. Oral Vancomycin (40 mg/kg/day divided QID, max 2 grams) may be required for multiply recurrent c. diff., although its use may predispose to VRE. In patients who have severe colitis, oral Cholestyramine (Questran) may help eradicate toxin after antibiotic course is completed.
Lactobacillus or cultured yogurt can help repopulate the gut with innocuous flora. Because of some rate of false negative; therefore, repeat testing of persistent diarrhea is indicated.

F) Herpes simplex mucositis/stomatitis:

Chemotherapy-induced mucositis may be aggravated by herpes simplex. These lesions may be in the mouth and/or esophagus. Lesions of mucositis should be cultured for herpes simplex, although empiric treatment may be indicated. Any neutropenic patient who develops swollen lips, with or without crusting lesions, should be cultured for herpes simplex and empirically treated with Acyclovir 10 mg/kg/dose q 8 h IV. A patient with mucositis known to have previous problems with herpes simplex should be started on the above dose of acyclovir prior to culture results. These patients are often already on prophylactic doses of acyclovir.

G) Varicella/Zoster:

Visceral dissemination occurred in about one-third of untreated immunocompromised patients (pneumonia, hepatitis, pancreatitis, encephalitis) with a mortality of about 25% before Acyclovir was available. These infections are especially severe if the absolute lymphocyte count (ALC = WBC x % lymph) is < 500/mcl or if chemotherapy (particularly steroids) is continued through the infection. **Intense abdominal pain** can precede varicella by several days. **Intense lumbosacral pain** (with or without fever or rash) is often a prodrome of herpes zoster.

**Prophylaxis:**

1) All newly diagnosed oncology patients should be tested at diagnosis (before blood product administration if possible) for varicella antibody titers. In seronegative patients with a defined exposure to varicella, passive immunization in indicated. Treatment currently is with either IV IgG 400 mg/kg or, if enrolled on study, with varivax (varicella immune globulin given as soon as possible, and within 72 hours of exposure. Efficacy is problematic if given beyond 96 hours after exposure. Exposure is defined as a face-face household contact, playmate contact, classroom or lunchroom contact, or hospital contact. A person is considered infectious with varicella starting 24 hours before the onset of rash and until all vesicles are crusted over (see Red Book).

**Treatment:**

2) **Acyclovir** should be given as soon as possible once pox are suspected or recognized. Acyclovir (1500 mg/M²/day or 50 mg/kg/day ÷ q 8 hours) is generally given IV until no new lesions appear. Depending on the patient's course, Acyclovir (or other oral anti-herpes drugs) may be continued for a full 10 days p.o. at 3000 mg/M²/day 4 x/day.

H) Fungal Infections – Prophylaxis and Full Treatment

For F & N lasting > 72 - 96 hours: begin **evaluation for fungal disease** (e.g. CXR and/or chest CT, urine culture for fungus, ophthalmologic exam, CT scan of
sinuses; may need CT/MRI of liver, spleen, kidneys and brain - to detect fungal “abscesses”). Empiric antifungal therapy (with voriconazole, micofungin, or occasionally Amphotericin) should be added after 72 – 96 hours febrile, depending on the patient's degree and expected duration of neutropenia. (< 25% of patients with autopsy-proven fungal disease had positive fungal cultures antemortem).

Current OHSU Guidelines for Fungal Prophylaxis, Empiric Treatment, and Culture + Treatment

Prophylaxis:

<table>
<thead>
<tr>
<th>Patient</th>
<th>Medication</th>
<th>Alternative (pt with hepatic disease)</th>
<th>Start</th>
<th>Stop</th>
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<tbody>
<tr>
<td>Allogeneic Transplant</td>
<td>Fluconazole</td>
<td>Amphotericin B / Abelcet (or AmBisome, if patient meets criteria, see pg 9)</td>
<td>With conditioning therapy</td>
<td>Day +75</td>
</tr>
<tr>
<td>Autologous Transplant</td>
<td>Fluconazole</td>
<td>Amphotericin B / Abelcet (or AmBisome, if patient meets criteria, see pg 9)</td>
<td>With conditioning therapy</td>
<td>ANC ≥ 500 for 3 consecutive days, AND mucositis resolved, AND not on steroids</td>
</tr>
<tr>
<td>Transplant Pt with GVHD &lt;13 yr</td>
<td>Voriconazole</td>
<td>Amphotericin B / Abelcet (or AmBisome, if pt meets criteria, see pg 9)</td>
<td>With conditioning therapy</td>
<td>Once patient is receiving steroids &lt;1 mg/kg every other day</td>
</tr>
<tr>
<td></td>
<td>≥13 yr: Posaconazole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML &lt;13 yr:</td>
<td>Voriconazole</td>
<td>Amphotericin B / Abelcet (or AmBisome, if pt meets criteria, see pg 9)</td>
<td>ANC &lt; 500</td>
<td>ANC ≥ 500 for 3 consecutive days</td>
</tr>
<tr>
<td></td>
<td>≥13 yr:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapsed ALL</td>
<td>Fluconazole*</td>
<td>Amphotericin B / Abelcet (or AmBisome, if pt meets criteria)</td>
<td>ANC &lt; 500</td>
<td>ANC ≥ 500 for 3 consecutive days</td>
</tr>
<tr>
<td>All Other Malignancies, With</td>
<td>Fluconazole</td>
<td>Amphotericin B / Abelcet (or AmBisome, if pt meets criteria, see pg 9)</td>
<td>ANC &lt; 500</td>
<td>ANC ≥ 500 for 3 consecutive days</td>
</tr>
<tr>
<td>Anticipated Neutropenia ≥15 Days</td>
<td>Voriconazole</td>
<td>Amphotericin B / Abelcet (or AmBisome, if pt meets criteria, see pg 9)</td>
<td>See specific underlying malignancy “Start”</td>
<td>See specific underlying malignancy “Stop” recommendation</td>
</tr>
</tbody>
</table>

*Fluconazole*
### Any Pt with History Of Previous Candidal Infection

<table>
<thead>
<tr>
<th>Medication</th>
<th>ANC &lt; 500</th>
<th>ANC ≥ 500 for 3 consecutive days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphotericin B / Abelcet (or AmBisome, if pt meets criteria, see pg 9)</td>
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**Empiric Antifungal Therapy for Prolonged F & N: * **

<table>
<thead>
<tr>
<th>Risk for Mold and History of Recent Azole Exposure</th>
<th>Medication</th>
<th>Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk for mold, no recent exposure to azoles (and not receiving fluconazole prophylaxis)</td>
<td>Fluconazole</td>
<td>Micafungin</td>
</tr>
<tr>
<td>Low risk for mold, recent exposure to azoles</td>
<td>Micafungin</td>
<td>Amphotericin B / Abelcet (or AmBisome if pt meets criteria, see pg 9)</td>
</tr>
<tr>
<td>High risk for mold, no recent exposure to azoles</td>
<td>Voriconazole</td>
<td>Amphotericin B / Abelcet (or AmBisome if pt meets criteria, see pg 9)</td>
</tr>
<tr>
<td>High risk for mold, recent exposure to azoles</td>
<td>Amphotericin B / Abelcet (or AmBisome if pt meets criteria, see pg 9)</td>
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</table>

*Prophylactic fluconazole should be discontinued when beginning empiric antifungal therapy

Empiric Antifungal Therapy can be discontinued when the patient meets the 3 following criteria:
- A negative diagnostic evaluation for IFI **and**
- ANC >500 for 3 consecutive days **and**
- Afebrile for >48 hours

**Invasive Aspergillosis:**
- Start with IV voriconazole at 7mg/kg/dose q12 (no loading dose).
• May consider initial combination therapy of micafungin + voriconazole until a therapeutic voriconazole trough has been documented.
• Consider sending blood or BAL fluid for galactomannan assay.
• Further guidelines are on Peds - PHO X drive – PHO staff can access.

III. TUMOR LYSIS SYNDROME (TLS)

Metabolic Triad of:

Hyperuricemia
hypoxanthine → xanthine → uric acid

Hyperphosphatemia
↑ PH04 → ↓ Ca++

Hyperkalemia

TLS is caused by the rapid release of intracellular metabolites when chemotherapy-induced cell lysis occurs. Each of the metabolic derangements can occur as an isolated problem or in combination. Uric acid and hypoxanthine crystals can precipitate in the kidneys and cause renal damage with hypertension or oliguria. Hyperphosphatemia is usually accompanied by hypocalcemia, with or without oliguria. Hyperkalemia is rare as an isolated problem but can occur when oliguria results from hyperuricemia or hyperphosphatemia. TLS is most commonly seen in patients with large burdens of tumor whose cells have very rapid doubling times and are very sensitive to chemotherapy, particularly Burkitt's lymphoma and acute leukemias. It is occasionally observed prior to treatment secondary to spontaneous cell lysis. When seen with leukemias, a very high white count and extramedullary disease is usually present (as in the T-cell ALL/lymphoma syndrome). TLS is virtually never seen in association with treatment of non-hematopoietic tumors such as rhabdomyosarcoma, osteogenic sarcoma, Wilms' tumor, and neuroblastoma, although isolated hyperuricemia can occur.

Management:

1) Institute precautionary measures necessary to deal with anticipated metabolic changes before chemo begins:
   a) Allopurinol (300 – 500 mg/M²/day divided TID; max 800 mg/day) to decrease uric acid production (xanthine oxidase inhibitor that reduces hypoxanthine and uric acid production). Because of its expense and potential immunogenicity, Rasburicase (recombinant urate oxidase - converts uric acid to more soluble allantoin, and thereby decreases levels of relatively insoluble hypoxanthine) should be reserved for patients with elevated uric acid and/or creatinine: 0.15-0.2 mg/kg/dose IV x 1 (1.5 mg vials); may repeat ≥ q 24 hours x 3 – 7 days for increased uric acid. If Rasburicase is given, alkalinization is not required; tumor lysis labs should be sent on ice so the Rasburicase in plasma sample does not reduce uric acid level spuriously. Allopurinol can be continued if massive lysis is expected. [Rasburicase is contraindicated in patients with possible G6PD deficiency, as it will induce hemolysis.]
b) Hydration at 1½ - 2 x maintenance IV with D₅ 1/4 NS plus 30 - 40mEq sodium bicarb/liter (as long as oliguria not present). Withhold KCl until serum K level < 3.0 mEq/L. Hydration may need to be increased to keep urine output adequate at 2-3 cc/kg/hr. Mannitol 0.5g/kg (max 25 g) q 6-12 h should be started 1-2 days before chemotherapy begins if significant TLS is anticipated, and increased to q 6 h once chemotherapy starts, with increased IV hydration as indicated. Mannitol helps excrete PO₄, K, (and Mg) through the proximal tubules. Furosemide IV (≥ 1 mg/kg q 4-8 h) may be used in addition for oliguria, working at the distal tubules.

c) Alkalinization with sodium bicarb as indicated in b) above to keep urine pH ≥ 6.5 and ≤ 7.5. Uric acid is most soluble within that pH range; urine pH > 7.5 can allow precipitation of hypoxanthine and calcium phosphate crystals. Stop alkalinization once serum phosphorus is elevated.

d) Use phosphate-binders like Sevelamer (Renogel) 20-40mg/kg/dose TID to decrease phosphate absorption if serum phosphorus elevated or elevation anticipated. Place on low phosphate diet (no milk products). Calcium carbonate (Tums) 10-25 mg/kg/dose TID may be useful if hypocalcemia is present in addition or instead of Sevelamer to bind PO₄ and provide small amounts of calcium.

e) Consider renal ultrasound to assess degree of tumor infiltration or uric acid/phosphate precipitation or possible ureteral obstruction from lymphadenopathy.

f) Consult nephrology early if the chance of severe tumor lysis syndrome appears high.

2) Monitor renal function and metabolic status closely once chemo has begun:
   Electrolytes, creatinine, uric acid, calcium, phosphorus at least BID; strict I & Os, cc urine output/kg/4-6 hrs, daily or BID weights.

3) General indications for hemodialysis

a) K⁺ > 6.5 mEq/L: treat emergently with calcium gluconate, sodium bicarb, insulin, glucose, follow cardiac monitor, IV Furosemide may be helpful. (Administer oral Kayexalate for K⁺ > 6 mEq/L.) Occasionally in patients with very high white counts, a falsely elevated K is reported by the central lab, as the WBC in the blood tube autolyse and raise the serum K⁺ level. Running the serum K⁺ STAT on the ICU machine may be helpful. However, when in doubt, assume the elevated K is real.

b) Tetany or severe neurological symptoms secondary to hypocalcemia: give small calcium boluses for these symptoms, risking increasing the calcium: phosphorus product. Consider use of oral calcium carbonate (Tums) (20-65 mg/kg + QID) to provide Ca²⁺ and bind PO₄.

c) phosphorus > 10 mg/dl or calcium: phosphorus product > 60 mg/dl. Discontinue alkalinization since calcium phosphate crystals are less soluble at urine pH > 6. Alkalosis decreases ionized calcium and can increase tetany. If phosphorus and uric acid both elevated, consider use of
Acetazolamide (Diamox) 5mg/kg/dose BID-TID p.o. or IV, as this drug will acidify serum and alkalinize urine.

d) uric acid > 15 mg/dl

e) creatinine > 3 mg/dl

f) oliguria with volume overload despite repeated large doses of Furosemide or Mannitol: may consider low dose Dopamine prior to instituting hemodialysis.

IV. SUPERIOR VENA CAVA (SVC) AND SUPERIOR MEDIASTINAL SYNDROMES:

SVC Syndrome is caused by compression or obstruction of the SVC. It is often part of the superior mediastinal syndrome (SMS) that involves tracheal compression and respiratory compromise as well. It occurs at presentation in about 15% of pediatric malignant anterior mediastinal tumors (Non-Hodgkin’s Lymphoma involving the lymph nodes and thymus surrounding the SVC is the most common malignancy). Pleural and/or pericardial effusions may co-exist. Progressive vascular compromise may result in thromboembolic phenomena, extreme increases in intracranial pressure, or decreased cardiac output. Progressive tracheal and bronchial compromise can result in respiratory failure. Pericardial effusions or direct cardiac compression by tumor can impede cardiac output or cause cardiac tamponade and require emergency pericardiocentesis.

Symptoms of SVCS and SMS (usually progresses rapidly in children):

Cough, hoarseness, dyspnea, orthopnea, chest pain, headache, visual impairment, and lethargy.

Signs:
Swelling, plethora, and cyanosis of face, neck and upper extremities; suffusion and edema of conjunctiva; distended neck and chest wall veins; diaphoresis; wheezing; stridor; pulsus paradox.

Diagnosis: is made by history, physical, chest x-ray/chest CT scan, and echocardiogram

Management (malignancy is presumed cause):

1) Assess airway compression and cardiac status: PE, O2 sat, emergency echocardiogram

1) Tissue diagnosis: make diagnosis by least invasive procedure possible. And do not attempt to make any diagnosis if there is any risk of intubation as a result!

a) CBC may show leukemia associated with mediastinal mass (as in T-cell ALL/Lymphoma syndrome).

b) Thoracentesis often provides diagnostic material in the case of Non-Hodgkin’s Lymphoma.
c) Bone marrow aspirate and biopsy may reveal leukemia or marrow involvement with lymphoma.

d) Peripheral node biopsy (supraclavicular, cervical, etc.) if local anesthetic tolerable.

2) **Avoid anesthesia or heavy sedatives.**

   The supine position may further impede venous return or air flow. General anesthesia decreases respiratory muscle tone, relaxes bronchial smooth muscle, and decreases lung volume. Anesthesia and heavy sedatives can impede venous return and decrease cardiac output by causing peripheral vasodilatation. Extubation may be impossible following anesthesia until tumor bulk is reduced.

3) **Delay definitive diagnosis** if necessary.

   In addition to the above studies listed in 1), obtain serum for alpha fetoprotein and beta HCG (germ cell tumors rarely may cause SVCS/SMS), along with uric acid and LDH. Chest CT scan to define mass should be done when patient clinically stable if diagnosis of lymphoma in doubt.

4) **Emergency Steroids**

   Emergency steroids (Methylprednisolone 5 - 16 mg/M2/dose q 8 hours; Dexamethasone 0.5 - 2 mg/kg/dose q 8hrs) may be necessary to rapidly reduce symptoms. (Tumor lysis syndrome may inevitably develop following steroid treatment.)

5) **Respiratory and circulatory support:**

   ICU management is often initially warranted: O2, bronchodilators, steroids, thoracentesis, pericardiocentesis, CVP line; begin chemotherapy as soon as possible (managing TLS as well – often with dialysis). Mechanical ventilation only if no other management choice remains.

6) Evaluate for intraluminal thrombosis if SVCS/SMS does not resolve with radiation therapy, steroids, or chemotherapy within several days.

V. **HYPERLEUKOCYTOSIS (WBC >100,000/mcl):** Seen at presentation in 10 to 15% of patients with ALL or AML. Complications result from leukostasis, microthrombi, and hyperviscosity. CNS and pulmonary problems are most common. Signs of hyperviscosity include blurred vision, confusion progressing to stupor, labored breathing, and hypoxia. CNS or pulmonary hemorrhage or thrombosis and priapism can also occur. Blood viscosity depends on the packed red cell volume and the packed leukocyte volume. Myeloblasts are large cells: 350 to 450 microns in diameter; lymphoblasts are smaller (250 to 350 microns). Thus, hyperviscosity syndrome is more commonly seen with hyperleukocytosis of AML than of ALL.

**Management**

1) Institute precautionary measures of tumor lysis syndrome management: hydration, alcalinization, allopurinol, etc.
2) If platelets <20,000/mcl, transfused with platelets (to prevent hemorrhage).

3) Delay transfusion with packed red cells until WBC <100,000/mcl, unless signs of cardiovascular decompensation secondary to anemia are present. Partial exchange transfusion to correct anemia or leukopheresis with pRBC and plasma if congestive heart failure present.

4) Institute emergency leukopheresis if signs/symptoms of leucostasis or hyperviscosity are present. This procedure is not always effective at significantly decreasing WBC, particularly if blasts have very rapid doubling times. (Leukopheresis is generally not indicated purely as a means to prevent/diminish tumor lysis syndrome.)

5) Institute chemotherapy as soon as the patient is metabolically ready, or dialysis support is in preparation.

BLOOD PRODUCT SUPPORT

I. Hypoproduction Anemia

A) Indications for pRBC transfusions:
The decision to transfuse should be based on clinical assessment and not on Hgb or Hct alone. Patient with chemotherapy-induced hypoproduction anemia or anemia secondary to bone marrow infiltration generally tolerate lower Hgb than do patients with acute blood loss or hemolysis, as the cardiovascular system has had more time to compensate in the former situation. The usual rate of decline in Hgb is 1 g/dl per week if the anemia is purely from hypo-production (a faster decline suggests blood loss, splenic sequestration, infection, or hemolysis).

B) Criteria for pRBC transfusion:
1) Symptomatic anemia: significant tachycardia, gallop, light-headedness, malaise, irritability, congestive heart failure: very unusual with Hgb ≥ 7 g/dl in child and ≥ 8 in adolescent.

2) Hgb < 7 g/dl: tissue oxygen delivery is usually suboptimal. Patients with elevated retic counts or nucleated red blood cells seen on smear may not need to be transfused.

3) Hgb < 9 g/dl at start of intensive course of in-patient chemotherapy. For the convenience of not having to transfuse the patient as an out-patient one or two weeks later, consider transfusing such patients before discharge, as the expected decrease in Hgb of 1 g/dl per week will result in a Hgb of < 7 g/dl at the time of nadir two weeks later.

4) Hgb should generally be kept ≥ 10 g/dl during radiation therapy to maximize RT efficacy.

C) Volume and rate of pRBC transfusion:
Standard transfusion volume = 10 – 15 ml/kg (this amount will increase the Hgb by 2.5 to 3.5 g/dl if the Hct of pRBC is 70%). This amount is usually cardiovascularly safe given over 3 hours if the Hgb is > 7 g/dl. If Hgb < 7 g/dl, transfusion volume = \( \frac{\text{Hgb}}{\text{kg body weight}} \) (e.g. 20 kg patient with Hgb = 5 g/dl would receive 100 ml over 3 hours and use Furosemide as indicated. Multiple transfusions, totaling about 400 ml will be required to bring Hgb to about 10 g/dl). Multiple transfusions should be separated by several hours to allow cardiovascular stabilization. The blood bank can split a pRBC unit so at least two transfusions are from the same donor if the volume to transfuse is < 150 cc. The volume of subsequent transfusions can be increased to 7 cc/kg and then 10 cc/kg. Partial exchange transfusion with pRBC is sometimes preferable to repetitive pRBC transfusions, particularly if congestive heart failure is present. By this method, anemia can be corrected rapidly and isovolumically. Total volume of exchange = \( \text{wt} \times 75 \times \frac{\text{HbD} - \text{HbW}}{22} \) (HbD = desired Hgb; HbW = average of desired and initial Hgb) with 5 cc/kg withdraw and replacement passes. Venous access may pose problems, however. Repeated 3 cc/kg pRBC transfusions preceded and followed by Furosemide is often a safe way to transfuse patients in congestive heart failure as well.

II. Hypoproduction Thrombocytopenia

A) Guidelines for platelet transfusions in hypoproduction thrombocytopenia:

1) Frank bleeding

2) Mucosal oozing or extensive bruising and petechiae (this is unusual if platelet count >10,000/mcl unless associated DIC or clotting factor deficiencies are present)

3) Prior to LP if plts < 10,000/mcl (rare complication of epidural hemorrhage)

4) Prior to invasive procedures: intubation, arterial line placement, CVP line placement, endoscopy, dialysis catheter placement, etc., if plts < 40-50,000/mcl (< 75,000/mcl before central venous line placement by peds surgery)

5) Febrile patients with plts <20,000/mcl

6) Plts < 10 -15,000/mcl and expected continued decline over next several days

7) Plts < 30-40,000/mcl in DIC (associated with sepsis or AML induction)

8) Plts < 50,000/mcl with large brain tumors or brain surgery in previous three months.

9) Plts < 50,000/mcl for 48h after major surgery (including dental extractions)

Most intracranial hemorrhages are associated with platelet counts < 5,000/mcl and rarely occur spontaneously without prior mucosal or cutaneous bleeding. The maximum platelet decline if due solely to hypoproduction is a decrease of 50% per day. A faster decline suggests consumption or sequestration.
B) Volume and rate of platelet transfusions – anticipated plt count rise at least 30K

   Infant: 10 cc/kg  
   Child 10 – 30 kg: ½ apheresis platelet pack  
   Child > 30 kg: 1 apheresis platelet pack (occasionally 2 packs for large adolescent)

C) Transfusion reactions

Fever and shaking chills can occur in reaction to platelet transfusions. The proteins in the plasma of platelet packs are the most likely cause, and not an infected unit, although the latter occasionally occurs. Pretreatment with Benadryl (1 mg/kg) and Tylenol or Ibuprofen often prevents these reactions. Occasionally hydrocortisone, 50-100 mg IV, is also needed. Treatment with Benadryl or Demerol (1 mg/kg) usually stops the reaction. Transfusion can usually be resumed, provided the reaction stops following treatment. If anaphylaxis requiring epinephrine occurs, that product should not be resumed; that donor should be marked as unacceptable for that patient. The possibility of an infected unit should be considered.

III. BLOOD PRODUCTS SPECIFICATIONS:

   A) Irradiated products: irradiated pRBC and plts are required for all oncology patients (2500 cGy). Irradiation inhibits leukocyte proliferation, thus preventing graft-versus-host disease (GVHD) in immuno-compromised hosts.

   B) Leukodepletion: pRBC and apheresed plts are leukodepleted in the blood bank for all oncology patients. This procedure reduces exposure to HLA antigens, and refractoriness to platelet transfusions, and helps prevent transfusion reactions caused by leukocyte antigens (fever, chills, hives). It also decreases transmission of CMV.

CHEMOTHERAPY

I. Agents Generally Requiring Hospitalization for Administration

The vast majority of chemotherapy is given in the out-patient Heme-Onc Clinic. Chemotherapy requiring hospitalization include:

   1. Continuous infusion Doxorubicin (Adriamycin) or Daunorubicin in patients with internal reservoirs (extravasation causes severe tissue necrosis).

   2. High-dose Methotrexate (3-12 g/m²) with hydration, alkalinization, and Leucovorin (folinic acid) rescue and antiemetics. MTX levels and urine PH and output need to be monitored closely to prevent toxicity.

   3. Ifosfamide with hydration, repeated doses of Mesna (sulphhydril uroprotector), and antiemetics.
4. Very high-dose Cyclophosphamide (Cytoxan) with hydration, repeated doses of Mesna and antiemetics.

5. Cis-Platin with hydration; forced Mannitol diuresis; magnesium, calcium, potassium IV supplementation, antiemetics.

6. High-dose Cytarabine (Ara-C), with frequent ophthalmic drops to prevent conjunctivitis and antiemetics.

A) Doxorubicin (Adriamycin)
Antibiotic inhibits DNA replication. Severe tissue necrosis occurs if skin or subcutaneous extravasation occurs, thus requiring hospitalization for prolonged infusions. Cumulative doses can lead to irreversible cardiomyopathy. Echocardiograms are performed periodically to assess left ventricular function and changes in ejection and shortening fractions. Causes mucositis, nausea, vomiting, diarrhea, myelosuppression, and radiation recall (should not be administered concomitant with XRT.) Urine is often reddish-orange following administration. Dose reduction is required if bilirubin is elevated.

B) Methotrexate (MTX)
Folic acid analog: suicide substrate for dihydrofolate reductase. Dose limiting toxicities include myelosuppression and mucositis. Other side effects include nausea, vomiting, alopecia, hepatic injury (usually reversible), skin photosensitivity, glomerular damage. Methotrexate can accumulate in ascites, edema, and effusions which can result in prolonged toxicity, and should never be given if such fluids are present. Administration of high-dose Methotrexate (3 to 33 gm/M²) requires good renal function (determined by calculated creatinine clearance). Hydration with NaHCO₃ to promote alkalinization is required during and following Methotrexate administration. Leucovorin (folinic acid) rescue and serial serum Methotrexate levels are also required (see MTX excretion curve and leucovorn requirements below). Prophylactic Septra should be held during Methotrexate/Leucovorin administration.
C) Ifosfamide
Alkylating agent similar to Cytoxan; converted to active metabolite in liver.
Hemorrhagic cystitis caused by Ifosfamide is much more severe than that of Cytoxan. Co-administration of Mesna along with good hydration following Ifosfamide administration is always necessary. Has been associated with CNS symptoms of altered mental status, cerebellar and cranial nerve dysfunction, and seizures (may be exacerbated by sedative effect of anti-emetics). Can cause renal tubular damage with HCO₃, PO₄ and K wasting and renal rickets. Other side effects include nausea, vomiting, alopecia and myelosuppression.

D) Cyclophosphamide (Cytoxan: CTX).
Alkylating agent; inert until converted to active metabolite in liver. Myelosuppression is dose-limiting toxicity. Hemorrhagic cystitis is the main non-hematologic toxicity and requires good hydration (to dilute bladder concentration of toxic metabolites) before and after Cytoxan administration to prevent this. Some protocols require co-administration of the sulfhydryl uroprotector Mesna, for which patients usually need hospitalization. Other side effects include nausea, vomiting, SIADH (transient), alopecia, exacerbation of Adriamycin cardiotoxicity, pulmonary fibrosis (long-term).

Fig. Plasma MTX concentration as a therapeutic guide to high-dose MTX therapy with citrovorum factor rescue. Citrovorum is continued until the plasma MTX level is less than $1 \times 10^{-7}$ molar. Each dose of citrovorum is increased if the plasma MTX concentration is excessively high, according to the nomogram. With 4-6 hr high-dose MTX infusions, plasma drug values in excess of $10^{-3}$ and $10^{-6}$ molar at 24 and 48 hours after starting the infusion, respectively, are often predictive of delayed MTX clearance.

Note: $1 \times 10^{-4} = 100 \ \mu$molar; $1 \times 10^{-5}$ molar = 10.0 $\mu$molar; $1 \times 10^{-6}$ molar = 1.0 $\mu$molar; $1 \times 10^{-7}$ molar = 0.1 $\mu$molar; $5 \times 10^{-8} = 0.05 \ \mu$molar.
E) **Cis-Platin**

Alkylating agent; cross links DNA. **Nephrotoxicity** is dose-limiting toxicity. Glomerular injury causes reduced GFR; renal tubular injury causes wasting of magnesium, calcium, potassium. Calculated creatinine clearance should be greater than about 60 before giving cis-Platin. Prolonged hydration with forced Mannitol diuresis is necessary to enhance renal excretion following cis-Platin administration. Magnesium, calcium, and potassium IV supplementation is often necessary. Chronic oral supplementation with magnesium and potassium is often necessary as well. Cis-Platin causes irreversible ototoxicity (high-frequency hearing loss) which should be monitored with serial audiograms. Other side effects include severe nausea and vomiting, peripheral neuropathies and myelosuppression. **Do not use aminoglycosides or furosemide in a patient who recently received cisplatin unless there is no alternative.**

F) **Cytarabine (Ara-C)**

Pyrimidine analog; acts as “false base” for DNA. Myelosuppression and neurotoxicity are dose-limiting. Conjunctivitis must be prevented with isotears or similar ophthalmic drops every 2 hours while awake, during and x 12 hr after infusions of ≥ 1 g/m². Cytarabine may cause fever during and up to 36 hours after the infusion. Rashes, including severe skin desquamation may occur. Maintenance hydration is adequate during high-dose Ara-C. Emesis can be moderate at high-doses.

II. SELECT TOXICITIES OF CHEMOTHERAPY

**Anaphylaxis:**
- VP-16 (Etoposide), L-Asparaginase, Carboplatin

**Cardiomyopathy:**
- Doxorubicin, Daunorubicin, Idarubicin, Mitoxantrone

**Coagulopathy; thrombosis:**
- Asparaginase

**Constipation/ileus:**
- Vincristine, Vinblastine

**Fever** (within 24-36 hours of dose):
- Vincristine, Ara-C (often associated with rash, conjunctivitis, arthralgias: “Ara-C Syndrome”)

**Glomerular toxicity:**
- Cis-Platin, Methotrexate, Carboplatin

**Hemorrhagic cystitis:**
- Cyclophosphamide, Ifosfamide

**Hepatitis:**
- Methotrexate, 6-MP, 6-TG, Asparaginase
Hyperglycemia – insulin-dependent (usually reversible):  
Asparaginase, Prednisone, Dexamethasone

Mucositis:  
Methotrexate, Adriamycin, Daunomycin, Actinomycin, Ara-C (high-dose), Etoposide (high dose)

Ototoxicity:  
Cis-Platin (worsened with concomitant/subsequent use of furosemide and aminoglycosides). **Do not use aminogycosides or furosemide in a patient who recently received cisplatin unless there is no alternative.**

Pancreatitis:  
Asparaginase, Methotrexate

Peripheral neuropathy:  
Vincristine, cis-Platin, Vinblastine, Etoposide (VP16), Taxanes

Pulmonary fibrosis:  
Bleomycin, Cyclophosphamide (high dose), Bulsulfan, CCNU, BCNU

Renal tubular damage:  
Cis-Platin (especially wasting of magnesium, potassium, calcium), Ifosfamide (especially wasting of bicarb, phosphorus, potassium, glucose [Fanconi’s syndrome])

Seizures:  
Vincristine, Ifosfamide, intrathecal (IT) or high dose IV Methotrexate, IT Ara-C

Seizures after IT MTX can occur up to several weeks later, and is probably related to folate depletion, increased homocysteine and increased excitatory neurotransmitters. IV leucovorin can reverse the folate deficiency and pectoral levels can decrease the neurotransmitters.

SIADH (transient):  
Vincristine, Cyclophosphamide, Ifosfamide

Tissue necrosis with extravasation:  
Vincristine, Adriamycin, Daunomycin, Actinomycin