Common Problems Encountered on M9

1. NAUSEA AND VOMITING

Introduction

- The most common and distressing acute toxicities of cancer chemotherapy
- Always rule-out other causes of vomiting (e.g. bowel obstruction, ileus, etc.)
- Vomiting may cause dehydration, electrolyte disturbances, weight loss, anorexia, aspiration, and patient non-compliances
- Emetic center is located in the lateral reticular formation of the medulla; it receives input from the:
  - Cerebral cortex
  - GI tract
  - Chemoreceptor trigger zone (CTZ) in the lower medulla
  - Dopamine receptors of the CTZ are activated by chemicals in the blood and CSF
- Peak plasma levels of chemotherapeutic agents are more closely related with emesis than is the total drug dose
- Individual patients with the same plasma levels of an emetogenic drug may or may not vomit, this may be due to the differences in the sensitivities of their CTZ
- There is significant patient to patient variation in the effectiveness and toxicity of each antiemetic drug
- N/V are more effectively handled if the patient takes antiemetics before the symptoms appear (When emesis is expected the dopaminergic receptors should be blocked before the chemotherapy stimulus affects the CTZ)

Therapy (Only a guideline)

Dexamethasone:	up to 30 mg/m^2 IV X one dose
Hydroxyzine:	1 mg/kg/dose IV/PO Q4-6h prn
Ondansetron:	0.15 mg/kg/dose X 3 doses (1 prior and 2 post chemo) **Or**
	0.15 mg/kg load, followed by 0.45 mg/kg/24h (continuous drip)
Granisetron:	20 mcg/kg/dose; MAX 1 mg
Lorazepam:	0.025 mg/kg/dose

Emetogenic Potential of Single chemotherapeutic Agents

Class V - High (>90%)

Busulfan (as part of BMT regimen)	Dacarbazine ≥500mg
Carboplatin >500mg/m^2	Ifosfamide
Carmustine ≥200mg	Lomustine ≥60mg
Cisplatin	Mechlorethamine
Cyclophosphamide >1g/m^2	Melphalan >80mg/m^2
Cytarabine >500mg/m^2	

Class IV - Moderately High (60 – 90%)

Actinomycin D	Doxorubicin ≥75mg
Carboplatin >500mg/m^2	Lomustine <60mg
Carmustine <200mg	Melphalan 20-80mg/m^2
Cyclophosphamide 500-1000mg/m^2	Methotrexate ≥ 3g/m^2
Cytarabine 100-500mg/m^2	Mitomycin
Dacarbazine <500mg	Procarbazine

Class III - Moderate (30 –60%)

Asparaginase	Fluorouracil ≥1000mg
Methotrexate ≥100 to ≤250mg	Teniposide
Cyclophosphamide <500mg/m^2	Vinblastine
Doxorubicin >20 to <75mg	

Class II - Moderately Low (10 – 30%)

Bleomycin	Etoposide
Cytarabine ≤20mg	Fluorouracil < 1000mg
Doxorubicin ≤20 mg	Methotrexate <100mg

Class I - Low (<10%)

Chlorambucil	Thioguanine (oral)
Cyclophosphamide (oral)	Thiotepa
Busulfan	Vincristine

2. TRANSFUSION REACTIONS

Non-Hemolytic Transfusion Reactions

Febrile

- Occurs during or shortly after transfusion
- Are due to leukoagglutination or cytotoxic antibodies usually against leukocytes
- Fever, chills, diaphoresis
- Prevent by giving leukocyte poor blood products (e.g. washed RBC's)

Rx - Acetaminophen 10 mg/kg po
- Antihistamines (diphenhydramine 1 mg/kg IV)
- Steroids (Hydrocortisone 50 mg/m^2 IV)

Allergic

- Occurs during or shortly after transfusion
- Caused by antibodies against plasma proteins
- Urticarial rash, facial and or mucous membrane swelling
- May be prevented by giving washed or frozen PRBC's

Rx - Antihistamines (diphenhydramine 1mg/kg IV)
- Steroids (Hydrocortisone 50 mg/m^2 IV)

Anaphylaxis

- Anaphylaxis is rare (may be caused by IgG anti-A antibodies in recipients who are IgA deficient)
- Anaphylaxis in these patients will be prevented if they are given washed PRBC's with IgA deficient plasma

Rx - Airway and cardiovascular support
- ***IV fluids***
- Epinephrine (1:1000) 0.01 ml/kg s.c. If the patient is in shock, give (1:10,000) 0.1 ml/kg i.v.
- Steroids (Hydrocortisone 10 mg/kg i.v.)
- Antihistamines (diphenhydramine 1-2 mg/kg i.v.)

Hemolytic Transfusion Reactions

- Most often are due to ABO incompatibility which causes intravascular hemolysis
- Are usually due to clerical errors such as mislabeling of blood samples
- Fever, chills, tachycardia, flushing, apprehension, hypotension, shock, acute renal failure, DIC, chest, abdominal and lower back pain, nausea, vomiting, spherocytosis, positive Coomb's, hemoglobinuria, indirect hyperbilirubinemia

  Rx - IVF Hydration
  - Forced diuresis (furosemide)
  - Steroids, antihistamines
  - Treat shock
  - Treat DIC

3. MANAGEMENT OF THE FEBRILE AND NEUTROPENIC PATIENT

[**These are ONLY GUIDELINES, please discuss with Fellow and Attending on service**]

- Infection is the most common cause of death in children with cancer and neutropenia
- Classical signs and symptoms of infection are often absent in patients with neutropenia
- Since these patients are unable to produce an adequate inflammatory response, infection can disseminate rapidly and terminate fatally. **YOU MUST MAKE AN IMMEDIATE ASSESSMENT OF YOUR PATIENT'S HEMODYNAMIC STATUS. IMPENDING SHOCK REQUIRES EMERGENT INTERVENTION. DO NOT WAIT FOR THE PATIENT TO BECOME HYPOTENSIVE. RECOGNIZE THE SIGNS AND SYMPTOMS OF IMPENDING SHOCK:**
  - **Decreased perfusion: decreased urine output, clouded sensorium, cool extremities**
  - **Compensation for decreased perfusion: tachycardia, ultimately hypotension**
- About 85% of bacterial infections arise from endogenous flora colonizing the GI tract, Gram (-) bacilli [e.g. ***E. Coli, P. Aeruginosa, Klebsiella***] or skin, Gram (+) cocci [e.g. ***S. epidermidis, S. aureus, alpha-hemolytic streptococcus]***
- Most frequent site of infection are:
  - Skin (IV/CVL sites, cellulitis)
  - GI (stomatitis, typhlitis, enterocolitis, perirectal cellulitis)
  - Pulmonary (pneumonia)
- If you identify a specific site of infection, it will influence your choice of antibiotics. EXAMINE THE PATIENT CAREFULLY FOR A SOURCE OF INFECTION.
- Every neutropenic (ANC < 500) patient that develops fever should have a complete P/E and appropriate cultures taken (blood, throat, urine, stool, skin, ± CSF), CXR where indicated
- Your choice of antibiotics must be guided by:
  - History of previous infections, especially catheter related infections
  - Interaction with chemotherapy, for example, avoid aminoglycoside antibiotics in patients who are receiving cisplatin
  - Evidence of a site of infection, for example, a perirectal cellulitis/abscess would require improved anaerobic coverage

Broad-spectrum antibiotics should be started empirically for febrile neutropenic patients.

For gram positive and gram negative coverage:

Cefepime 150-mg/kg/day div Q8hrs; (MAX 6 g/day)

And **Amikacin** 15 – 22.5 mg/kg/day div Q8 hrs
(monitor Amikacin levels and adjust dosages accordingly)

Or *__Ciprofloxacin__ 15 –20 mg/kg/day div Q12 hrs; (MAX 800 mg/day). For patients receiving ototoxic regimens (i.e., cisplatin, carboplatin)

If anaerobes are suspected add:

Clindamycin 40 mg/kg/day div Q6-8 hrs; (MAX 2.7 g/day)

Or **Metronidazole** 30 mg/kg/day q6 hrs; (max 4 g/day)

If fever persist for > 48 hours,

Add **Vancomycin** 10 mg/kg/dose IV Q6 hrs; (MAX 2 g/day)
If patient is to receive 2 grams, then give 1g Q12 hrs

If it continues to persist for > 48 hours after Vancomycin, suspect fungal infections:

Add **Liposomal Amphotericin** 5 mg/kg/day

- Candidiasis is the most frequent fungal infection in neutropenic patients
- Early diagnosis is difficult because manifestations of infections are usually not evident and the organism grows slowly (if at all) in blood cultures
- If fever persists after 3 – 5 days of broad spectrum antibiotics, empiric treatment with Liposomal Amphotericin should be started
- For Aspergillus, add Liposomal Amphotericin

For systemic viral infections:

Herpes simplex	**Acyclovir** 750 mg/m^2/day div Q8 hrs
Varicella zoster	**Acyclovir** 1500 mg/m^2/day div Q8 hrs

*** Needs ID approval, call beeper 1100 or X 6-7810 or ID fellow on-call**

ONCOLOGIC EMERGENCIES

1. TUMOR LYSIS SYNDROME

Etiology

- Occurs in patients with a large cell burden of tumor exquisitely sensitive to chemotherapeutic agents (e.g. Burkitt's lymphoma, T-cell ALL with high WBC)
- It is a consequence of rapid release of intracellular metabolites
  i) Uric acid
  ii) Potassium
  iii) Phosphate

Hyperuricemia

- Results from degradation of purines released by fragmented tumor nuclei

Purine → ***Hypoxanthine*** → ***Xanthine*** → ***Uric acid***
" "
" "
Xanthine oxidase

- The progressive precipitation of UA crystals in the distal tubules may produce obstructive uropathy, oliguria, azotemia

Treatment

- 1) IV hydration 3000 ml/m^2/24h (0.45% NaCl)
  [Extracellular volume expansion to increase urate excretion]
- 2) $NaHCO_3$ 120-200 mEq/m^2/24h (Add 5—75mEq/L and titrate to keep urine pH > 7).
  [Alkalization of urine to maximize urate solubility]
- 3) Allopurinol 10mg/kg/24h div TID (up to 500/mg/m^2/24h)
  [Decreases urate production by competitive inhibition of xanthine oxidase]

Monitor (frequently)

- Lytes, BUN, Cr, Uric acid, Mg, Ca, P, I&O, BP, neuro exam

Hyperkalemia

- Results from acute tumor lysis and may worsen with developing acute renal failure secondary to Hyperuricemia or Hyperphosphatemia
- ECG – tented T waves, wide QRS
- **Treatment**
  1) Kayexalate 1-2 g/kg in 20% sorbitol po
  2) Ca Gluconate 10% 0.5 ml/kg over 10 min
  (Not in same line with $NaHCO_3$, may precipitate)
  3) $NaHCO_3$ 1-2 mEq/kg over 5-10min
  4) Glucose 0.5/kg/i.v. With reg. Insulin 0.25 u/g of glucose i.v over 30min

2. SYNDROME OF INAPPRORIATE ANTIDIURETIC HORMONE SECRETION (SIADH)

Etiology

- **Cyclophosphamide**, ifosfamide, vincristine, barbiturates, opiates

- Cerebral injury, abscess, hemorrhage
- Following brain surgery for midbrain tumors
  (DI may be present the first 3-5 days post-op with SIADH later)
- Leukemia, lymphoma, Ewing, brain tumors
- Pulmonary disease / assisted ventilation (less common)

Signs and Symptoms

- Fluid retention, water intoxication
- Non-specific symptoms (headache, irritability, muscle weakness, nausea)
- Confusion, seizures
- Absence of edema

Diagnosis

- Hyponatremia, hypoosmolality
- Concentrated urine relative to plasma
- Continued urinary excretion of Na (>20 mEq/L)
- Normal renal and adrenal function
- Improvement of hyponatremia and urine sodium loss by fluid restriction

Differential Diagnosis

- Adrenal insufficiency
- Na loss from diarrhea, vomiting, hypercalcemia
- CHF
- Nephrotic syndrome

Treatment

- Elimination of underlying disorder when possible
- **Mild SIADH (Na ≥ 125mEq/L)**
  Fluid restriction (50-60% maintenance)
  Maintenance Na intake
- **Severe SIADH (Na = 120-125 mEq/L)**
  Furosemide 1 mg/kg iv
  Replacement of urine loss with hypertonic saline
- **Life-threatening SIADH (Na ≤ 120 mEq/L)**
  Furosemide 1 mg/kg iv
  200 mL/m^2 of 1.5% NaCl to correct Na to 120 mEq/L in 6-8 h,
  Then more slowly to normal over 24 to 48 h

3. SPINAL CORD COMPRESSION

***Paraplegia for more than 24 hours may be irreversible.**

Etiology

- Direct extension of paravertebral tumors (NB, Ewings, rhabdo)
- Extradural lesion (metastasis, abscess, lipomatosis)
- Hematoma in thrombocytopenic patients resulting from an LP
- Intradural lesion (primary central nervous tissue tumors, drop mets from medulloblastoma, ependymoma, astrocytoma)
- Vertebral body collapse from osteoporosis (due to prolonged glucocorticoid therapy) or vertebral body metastasis

Signs and Symptoms

- Pain (central back pain, vague deep ache, radiating pain to the extremities, tenderness and/or irritability in infants)
- Weakness

- Sensory changes (sensory level, hyperesthesia)
- Bowel and bladder involvement (generally late findings, constipation and urinary retention precede incontinence)

Diagnosis

- Careful and complete neurological AND GENERAL physical examination
- MRI (with gadolinium if leptomeningeal involvement)
- CT, myelogram (if MRI contraindicated)
- Spine films (not usually helpful)
- Tissue diagnosis (laminectomy specimen, lymph node biopsy, BM)
- PFTs with high lesions
- LP usually contraindicated
- CONSULT Neurology, Neurosurgery, Radiation Oncology

Treatment

- Close monitoring- frequent neuro exam
- Pain relief
- Glucocorticoids
- Chemotherapy (disseminated neuroblastoma, lymphoma, germ cell tumor, some sarcomas)
- Radiation (for symptomatic lesions, advanced metastasis, bulky unresectable tumor)
- Surgical decompression indicated
  - to establish histological diagnosis
  - failure of chemo-radiotherapy or chemo-resistant tumors
  - loco-regional neuroblastoma
  - stabilization of vertebral body collapse to relieve pain
    - cord compression from bony fragments
- Physical therapy, stool softeners, bladder drainage