PEDIATRIC HEMATOLOGY-ONCOLOGY CASE-BASED LECTURE SERIES

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How to use this lecture

- This content is based on the inpatient management of commonly seen scenarios in pediatric hematology-oncology patients
- The content will be ideal for medical students, pediatric residents, and first-year pediatric hematology-oncology fellows
- Some definitions (when to stop antibiotics) may differ at different treating institutions, but attempt has been made to make information generalizable

How to use this lecture

- Main menu listed on left side of lecture to navigate between topics
- Use arrows below to change slides
- Hyperlinks on each page to navigate between pages, and for additional information on certain concepts
- Questions for participant in *blue/italics*
- Total of 4 cases
  - Should take about 15 minutes per case

Cases

1. Fever and Neutropenia
2. Tumor Lysis Syndrome
3. Nausea and Vomiting
4. Acute Chest Syndrome

CASE 1 – FEVER AND NEUTROPENIA

Location: Emergency Department

- HPI: 7 year old female previously diagnosed with standard-risk acute lymphoblastic leukemia (ALL) currently receiving chemotherapy now on day 15 of her protocol (last chemo received – vincristine, doxorubicin day 8)
- Presents to ED with a history of fever to 102.1, feels tired, decreased oral intake, no other symptoms
- Hematocrit (Hct) 25.4%, platelets (plt) 179, white blood count (WBC) 0.6 K, absolute neutrophil count (ANC) 83
- ER draws blood cultures, starts antibiotics

- *What else do you want to know?*

Get a thorough history

- History of present illness
  - Patient/parent focal complaints/concerns
  - Is the patient hydrated, any concerns about perfusion, respiratory status
  - Chills (symptom - feeling of cold/mild shivering) vs. rigors (sign – intense, uncontrollable shivering; often seen with worsening bacterial infection/sepsis; consider broadening antibiotics)
- Review of systems
  - No focal concerns or other symptoms, appears hydrated and perfused per family and ED physician
- Past medical history
  - Patient has a history of previous line infection with Coagulase-Negative Staph (CONS) which required a 14 day IV vancomycin course, and a history of Pseudomonas urinary tract infection (UTI) earlier during therapy
  - No recent surgery, but underwent lumbar puncture two weeks prior for intrathecal methotrexate

Physical exam

- Very important to attempt to localize infection in neutropenic patient
  - Localizing signs may be subtle (may not be able to develop erythema with low neutrophil count), so close attention should be given to mild signs
- Full exam including central line site area, perianal area, ear exam are normal, patient looks tired but is cooperative, vitals signs normal

- *Any other changes or studies at this point?*

Management – additional studies

- With history of UTI – and questionable age for reporting dysuria, obtain a non-catheterized urinalysis (UA) (+culture)
  - Lack of WBCs on UA does not rule out UTI while neutropenic
  - Should consider UA in all febrile neutropenic patients, but would not delay antibiotics for sample
  - DO NOT instrument neutropenic patient outside of special circumstances (high risk of infection with mucosal break). NO RECTAL TEMPERATURES.
- Other studies as symptoms direct (chest X-ray, respiratory viral panel, stool studies – clostridium difficile toxin, rotavirus assay, etc.)

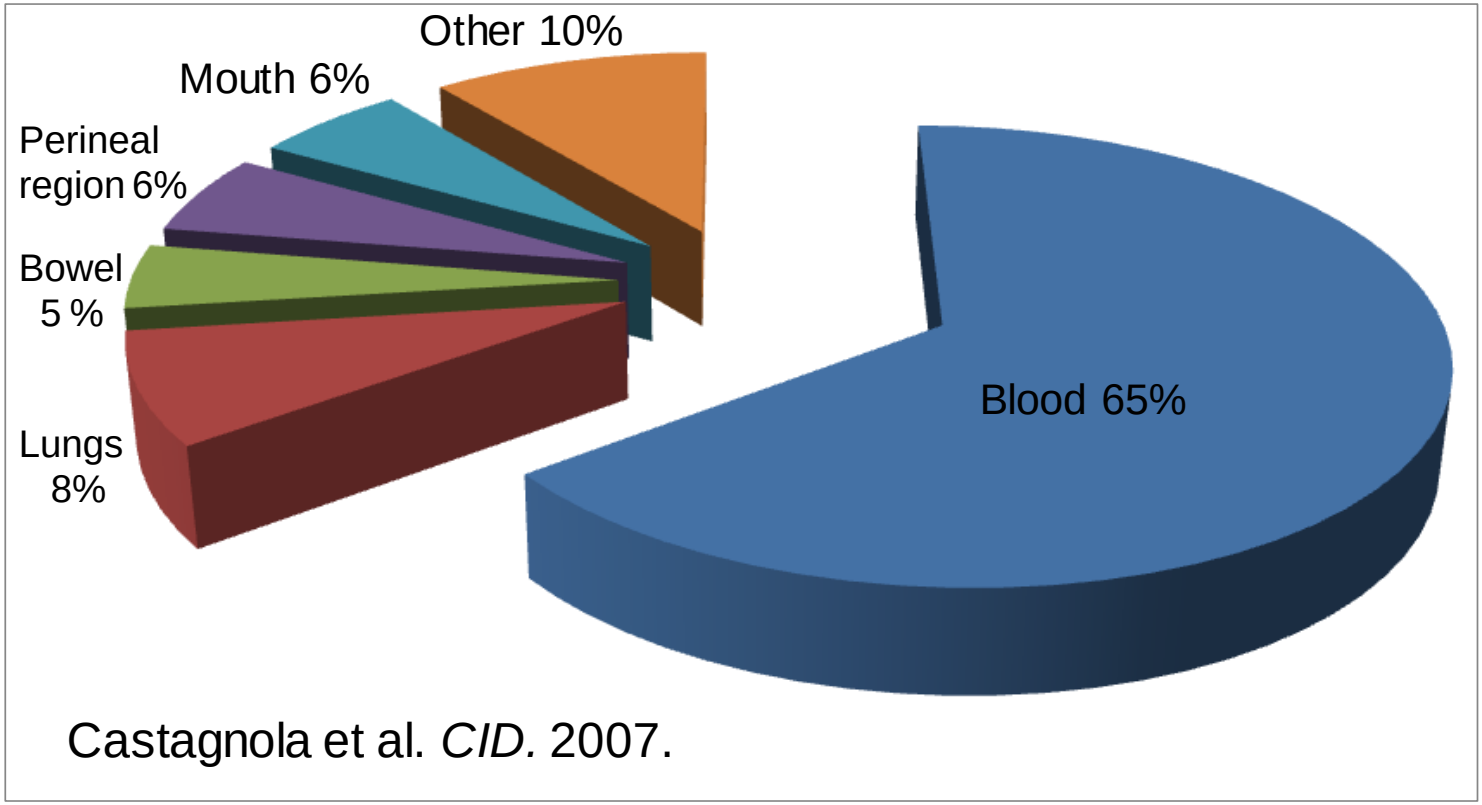
F + N – definition

- F(ever) = 38.3˚C (101˚F) one time (or 38.0˚C twice within defined time period, e.g., 8 or 24 hours, at some centers)
- N(eutropenia) = ANC < 500 (or 200 at some centers) OR predicted to fall below 500 in next 24-48 hours

- For febrile, non-neutropenic cancer patient with ill-appearance, treat as if neutropenic (immunosuppressed patient with indwelling central line is at high-risk for infection)

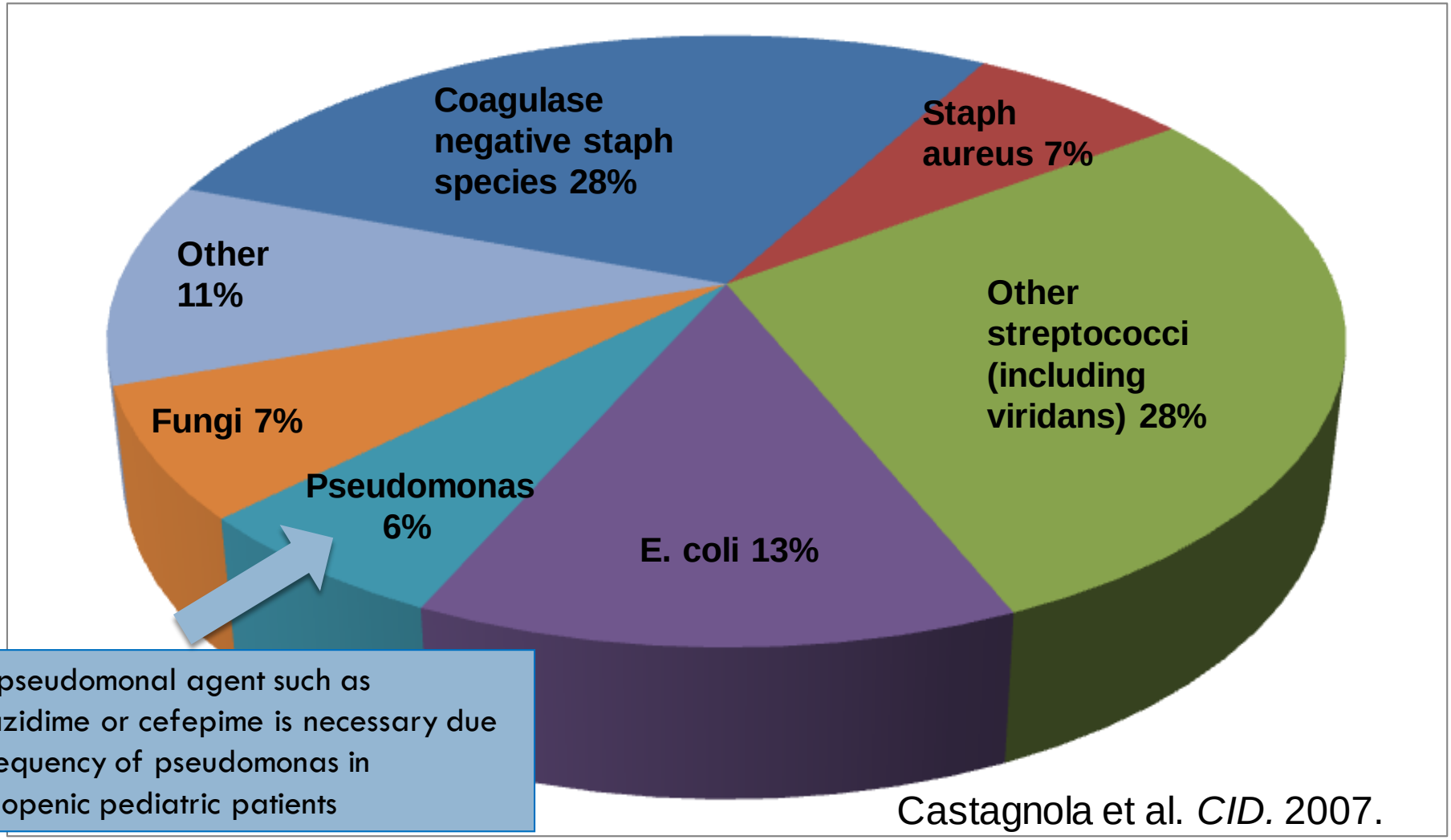
Location of documented infections

- Most (79%) have fever of unknown origin
  - Of the 21% with documented infection:



Castagnola et al. *CID.* 2007.

Isolated pathogens



Anti-pseudomonal agent such as ceftazidime or cefepime is necessary due to frequency of pseudomonas in neutropenic pediatric patients

Castagnola et al. *CID.* 2007.

Choice of antibiotic

- Start with cephalosporin with anti-pseudomonal activity (e.g., ceftazidime or cefepime depending on center), and add additional antibiotic(s) if situation arises:
  - Concern for abdominal or perineal infection: provide additional coverage for abdominal anaerobes
  - Severe mucositis: provide additional coverage for oral anaerobes
  - Hypotension, rigors, or other signs of hemodynamic instability: additional coverage for gram negative and positive infection in the setting of possible beta-lactamase resistance

Case 1 (cont)

- The patient is stable appearing after receiving one dose of antibiotic
- The medical student on service wonders if the (neutropenic) patient should empirically receive coverage for resistant gram positives, such as methicillin-resistant staph aureus (MRSA)

- *Are there additional antibiotics you would add?*

Adding vancomycin empirically

- Prospective trial of febrile neutropenic patients randomized for initial empiric therapy ceftazidime alone vs. ceftazidime plus vancomycin (Ramphal R et al. *Antimicrob Agents Chemother*. 1992.)
  - similar outcomes and survival rates; more renal and cutaneous toxicities in patients receiving vancomycin
  - Increased rates of VRE (vancomycin-resistant enterococcus)
- Most institutions DO NOT support adding vancomycin empirically for hemodynamically stable patients
  - History of previous line infection with resistant gram positive also DOES NOT mean the patient needs empiric vancomycin
  - Consider vancomycin if:
    - focal skin findings or severe mucositis
    - soft tissue pain beyond proportion of exam (sign of necrotizing fasciitis)
    - hemodynamic instability
    - Recent administration of cytarabine
  - Add vancomycin if blood culture shows gram positives (keep until susceptibilities further direct therapy)

Case 1 (cont)

- Day 3 of admission
  - Blood culture and urine culture have no growth to date (NGTD.) Patient has been afebrile for 36 hours.
  - Patient has ANC of 0.

  - *Can you stop antibiotics? If not, when?*
  - *Can you discharge the patient? If not, when?*

Stopping antibiotics / discharge

- Consider (there is considerable institutional variability) switching low-risk patients to oral antibiotics for discharge while neutropenic if the following are met:
  - Afebrile for 24 hours AND
  - Negative cultures for 48 hours AND
  - Well appearing, no concerning symptoms, can remain hydrated
  - Some centers also require minimum ANC or signs of marrow recovery – neutrophils or monocytes on differential
  - Regimens often contain an oral fluoroquinolone (sometimes with additional antibiotics) until recovery of counts
- Consider stopping antibiotics once patient has met above criteria and is no longer neutropenic by institutional definition (ANC > 200 or 500)

Case 1 - part 2 (6 months later)

- Patient has since developed relapse of his leukemia – is now getting treated with high dose cytarabine
- In clinic for evaluation, Hct 24, Plt 60, WBC 2.3, ANC 15. Febrile to 39.0°C.
- Patient well appearing, blood pressure (BP) 110/50, HR 110

- *What antibiotic to start?*

Viridans Group Streptococcus

- Important part of the normal microbial flora
  - Upper respiratory tract, gastro-intestinal tract especially oral cavity
- Common in cancer patients
  - Shock syndrome 10 - 25%
  - Mortality about 6 -12%
- Risk factors:
  - Female gender
  - High-dose cytarabine (included in AML and certain relapsed ALL re-inductions) OR clofarabine
  - Mucositis
  - Severe neutropenia
  - Prophylactic co-trimoxazole/quinolones
  - Poor dentition

Cefepime vs. Ceftazidime

Regimen	Activity against Viridans Streptococci
Cefepime	Excellent
Vancomycin	Excellent
Ceftazidime	Poor

Ceftazidime does not provide good coverage for Strep Viridans and therefore may not be the empiric agent of choice for patients at high risk for this infection. Cefepime will provide better coverage for patients at risk for this virulent organism.

Case 1 – part 2 (cont)

- Patient receives antibiotics – now appears drowsy, but just got benadryl for nausea. Vital signs: BPs 70s/20s. HR 150s. Cap refill (CR) 3 sec.

- *What do you want to do?*

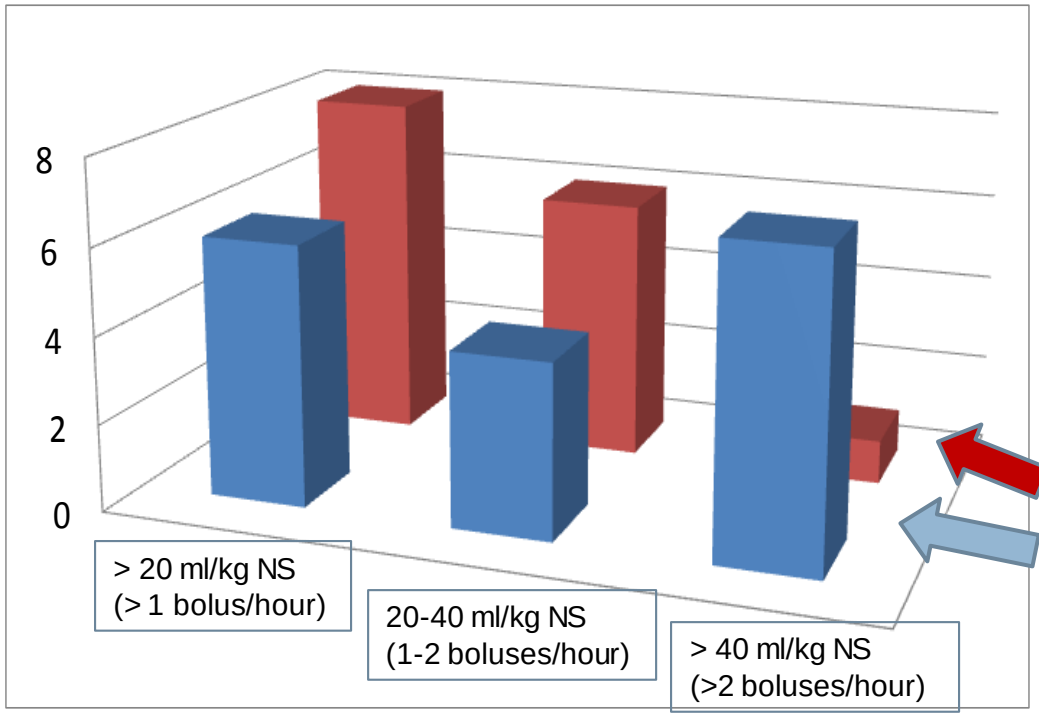
Case 1 – part 2 management

- Blood culture, urine culture (don't hold antibiotics), add additional coverage for resistant organisms (if not already started), normal saline (NS) bolus 20 ml/kg – all ordered stat, and verbalize plan with nurse (RN).

- *RN asks how to long to hang bolus over? When to re-assess fluid status?*

Fluid resuscitation in pediatric septic shock

• For pediatric patients with confirmed septic shock (positive blood culture, BP < 2 SD from mean, and tachycardia/poor perfusion), correlation between receiving >40 ml/kg normal saline (NS) (more than 2 boluses) in first hour and survival



Correct bolus schedule:
NS bolus 20 ml/kg over 20 minutes
- re-assess (5 minutes)
- next bolus (20 minutes)
- re-assess (5 min)
- repeat as needed

Carcillo JA. *JAMA*. 1991.

Case 1 – part 2 (cont)

- Day 7 - Patient stabilizes hemodynamically – all blood cultures were negative.
- Patient still intermittently febrile, but eating more and interacting with family.
- ANC still 0.

- *Any changes to regimen?*

Fungal coverage

- Persistent fever on 5-7 days therapy
  - Consider adding antifungal therapy
  - Voriconazole or Ambisome
    - Randomized trial of patients with fever and neutropenia for four days (Walsh TJ. *N Engl J Med*. 2002.)
      - voriconazole vs. ambisome (800 patients, 33 children)
      - voriconazole – less breakthrough infections, less infusion reactions, less renal toxicity (more hepatic toxicity), more transient visual disturbances and hallucinations than the ambisome
        - voriconazole/posaconazole are typically held (or switched to ambisome) a few days before and after administration of vincristine and/or anthracyclines due to interactions

Case 1 – part 2 (cont)

- Family has read that giving their son a Granulocyte-Colony Stimulating Factor (G-CSF) may hasten recovery of neutrophils – and wonders if this is an option.

- *Is there a role for G-CSF in this patient?*

G-CSF?

- G-CSF (Granulocyte-Colony Stimulating Factor) – medication administered subcutaneously or IV to encourage myeloid line proliferation
- Up front with chemo (primary prophylaxis)
  - Meta-analysis of 16 studies (Sung L et al. *J Clin Oncol*. 2004.)
    - CSFs were associated with 20% reduction in febrile neutropenia + two-day decrease in hospitalization duration
    - NO difference in parenteral IV antibiotic therapy + NO difference in infection-related mortality rate
  - ASCO guidelines – given if rate of fever and neutropenia with chemotherapy predicted to be greater than 20%

G-CSF once febrile?

- When patient becomes febrile
  - 67 patients randomized to antibiotics + G-CSF or antibiotics alone (Ozkaynak MF et al. *Pediatr Blood Cancer.* 2005.)
    - Group with G-CSF had faster resolution of neutropenia (4 days vs. 13 days), slightly shorter hospital stays (4 days vs. 5 days), but no difference in duration of fever, antibiotic therapy or incidence of shock
  - Controversial role, but considered if patient is very ill (intensive care, etc.) with prolonged neutropenia
    - For this well appearing patient, most oncologists would not add G-CSF, and would wait for natural recovery of neutrophils

REFERENCE SLIDES

Fever and Neutropenia Case

ALL chemotherapy

- ALL is treated in multiple stages of multi-agent chemotherapy (induction, consolidation/interim maintenance, delayed intensification, maintenance) usually over two to three years
- Patients may or may not be neutropenic throughout therapy depending on timing from last chemotherapy, response to chemotherapy, concurrent illness, and other factors

BACK TO CASE

Lab values

- Absolute Neutrophil Count (ANC) = total white blood cell count (cells/microL) x [percent polymorphonuclear leukocytes (PMNs) + percent bands)]
- Absolute Phagocyte Count (APC) = total white blood cell count (cells/microL) x (percent PMNs + bands + monocytes)

BACK TO CASE

Bacteria

- Coagulase-Negative Staph (CONS)
  - Gram positive bacteria, most commonly staph epidermidis, found as normal flora on skin; frequently isolated in blood stream infections in patients with indwelling catheters
  - Distinct (and less virulent) from (coagulase-positive) staph aureus
  - Frequently resistant to cephalosporins, often requires treatment with vancomycin
- Pseudomonas species
  - Frequently virulent gram negative bacteria, usually resistant to lower generation cephalosporins

BACK TO CASE

Normal vitals in children

age	Weight (kg)	HR	RR	Systolic blood pressure	Diastolic blood pressure
Newborn	3	100-160	30-60	50-70	29-45
6 mo	7	110-170	25-40	80-100	50-70
1-2 years	12	90-150	20-30	80-100	50-90
3-4 years	16	70-140	20-30	80-100	39-89
5-6 years	20	65-130	20-30	85-115	45-85
7-8 years	26	60-130	18-25	85-115	50-70
Adolescent	50	60-120	15-20	90-120	50-70

BACK TO CASE

REFERENCE MATERIAL

Fever and Neutropenia Case

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CASE 2 - TUMOR LYSIS SYNDROME

Location: Emergency Department

- 15 year old male presents to ED with fatigue and bone pain. CBC shows Hematocrit (Hct) 22%, Platelets 64K, white blood cell count (WBC) 60.8 K with 39% blasts.
- Uric acid 5.0 (normal 2-6), LDH 1555 (<700), K 3.6, Phos 3.8 (3-5.5) Ca 9.5 (8.5-10.5) Cr 0.7
- Patient is 77 kg

- *ER resident asks what you want for fluids/labs/any medications to start. . . .*

Tumor lysis prevention – the basics

- IV Fluids at 1.5 to 2 times maintenance rate – initial IVFs differ at different institutions (we will discuss choices later)
  - D5 ¼ NS (hypotonic)
  - D5 ½ NS (isotonic)
  - D5 ½ NS + 40mEq/L sodium bicarbonate (NaHCO3)
  - Do NOT add potassium (or use lactated ringer's, which includes potassium) with any concern for tumor lysis
- Consider medication for uric acid reduction (more on this later)
- Check "tumor lysis labs"
  - Electrolytes (lytes), BUN, creatinine (Cr), calcium (Ca), magnesium (Mg), phosphorous (Phos), uric acid, twice a day (or more)

Tumor lysis syndrome

- The electrolyte changes and clinical effects from rapid turnover and lysis of neoplastic cells
- Laboratory tumor lysis syndrome (LTLS) defined as two or more of the following:
  - uric acid ≥8 mg/dL (or 25 % increase)
  - potassium (K) ≥6.0 mmol/L (or 25 % increase)
  - Phos ≥6.5 mg/dL (or 25% increase)
  - Ca ≤7 mg/dL (or 25% decrease)
- Clinical TLS (CTLS)
  - LTLS + Creatinine increase to 1.5x normal, arrhythmia or seizure
- Bottom line – tumor lysis can result in:
  - Uric acid or CaPhos crystals in kidneys -> kidney failure
  - Elevated potassium /arrhythmia

Epidemiology

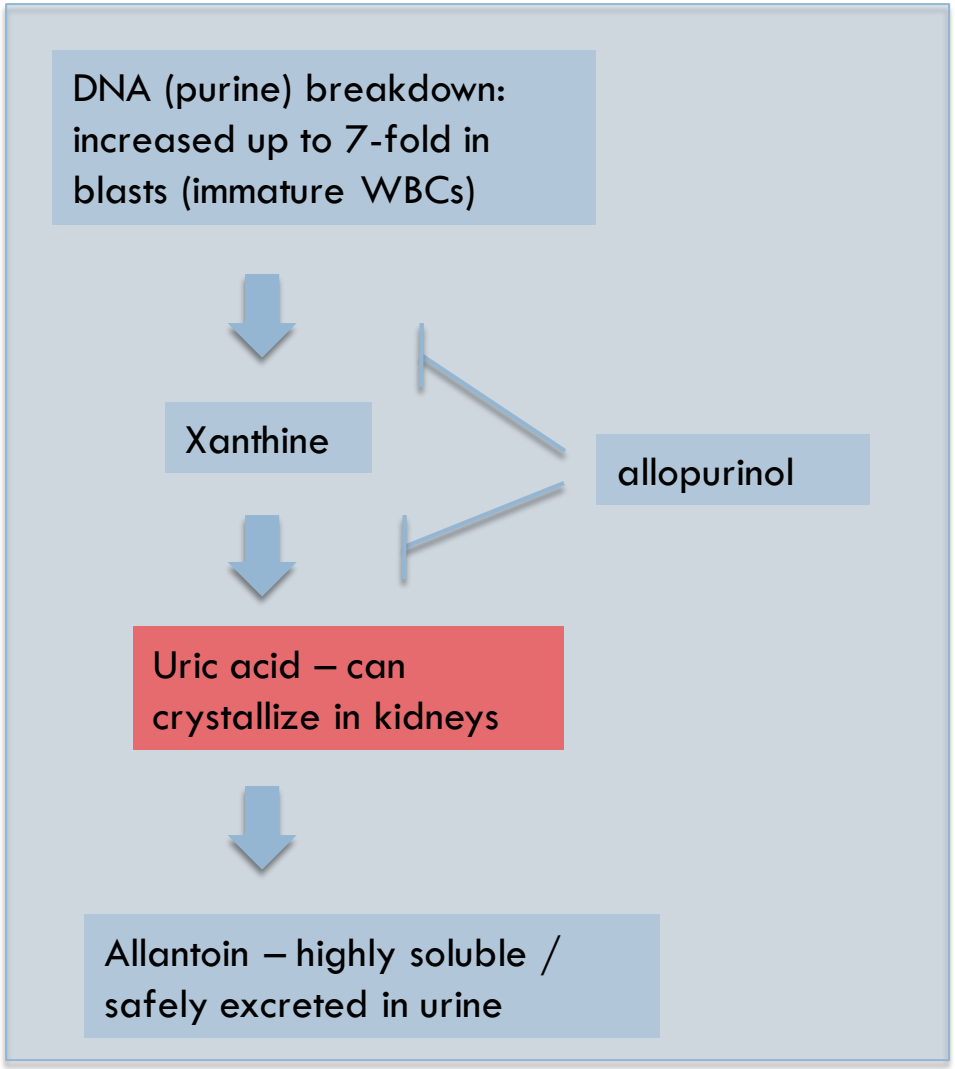
- Incidence of tumor lysis syndrome
  - Retrospective review of 788 oncology patients /332 children. (Annemans et al. *Leuk Lymphoma*. 2003).
    - Acute Myeloid Leukemia (AML) - 14.7% LTLS and 3.4% CTLS
    - Acute Lymphoblastic Leukemia (ALL) - 21.4% LTLS and 5.2% CTLS
    - Non-Hodgkin's Lymphoma (NHL) - 19.6% LTLS and 6.1% CTLS
  - Retrospective review of 614 AML patients during induction chemo (Mosteninos et al. *Haematologica*. 2008.)
    - 17% LTLS and 5% CTLS
    - LTLS not associated with death (p= 0.51)
    - CTLS associated with death (p=<0.001), cause of death in 14 patients

Prevention

- Fluid works: Increasing urine flow rate most important strategy
  - With high risk patient or elevated uric acid: Aim for 4 to 6 ml/kg/hr urine and Urine specific gravity <1.010
  - Be careful to not fluid overload patient (especially in context of mediastinal mass or severe anemia), by assessing that urine output is matched with fluid input
  - Use diuretics (furosemide increases the excretion of potassium and uric acid) as hemodynamics allows
- Increased urine ph with $NaHCO_3$ – theoretically increases uric acid solubility in urine
  - 15 mg/dl at urine ph of 5
  - 200 mg/dl at urine ph of 7
  - This effect is only theoretic: In mice models, increasing urine pH DOES NOT prevent uric acid crystals
    - $NaHCO_3$ carries with it risks (discussed below)

Allopurinol

- Efficacious
  - When used prophylactically in children at risk for tumor lysis, prevents increase in uric acid in 92% of children
- Well tolerated
  - Side effects – rash/allergy in < 10% patients
- Why not?
  - Increases uric acid precursors that may also form crystals
  - Use is center-dependant



Case 2 (cont)

- Patients' bone marrow shows blasts on smear.

- *Parents have read about tumor lysis online and are asking if their son is at high risk for tumor lysis syndrome when treatment starts.*

Risk factors for tumor lysis syndrome

- Tumor
  - Lymphoma
  - ALL/AML
  - Solid tumors with fast proliferation and response to treatment
- Baseline clinical status
  - Bulky disease
  - Elevated uric acid/LDH, WBC (>25,000)
  - Oliguria, elevated creatinine
- This patient has a leukemia with an elevated WBC and LDH, but normal kidney function and uric acid, so is at a moderate risk when treatment starts

Case 2 (continued)

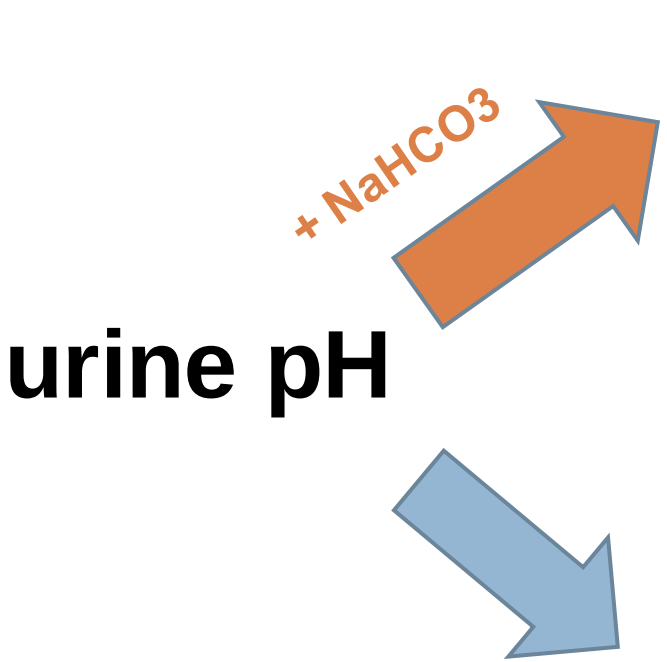
- Patient on IVFs at 200 ml/hr
- Treatment hasn't begun
- TLS labs come back:
- Uric acid 5.0 (nml 2-6), LDH 3800 (<700), K 3.8, Phos 6.0 (3-5.5) Ca 10.0 (8.5-10.5) Cr 0.8

- *Any changes you want to make?*

Watch out for the phos!

- Ca and phos rising – elevated Calcium and phosphorous can lead to CaPhos crystals in urine
  - Risk can be estimated sum of serum Ca x serum Phos
    - Ca x Phos > 50, at higher risk for CaPhos crystals
  - In order to decrease risk:
    - Discontinue NaHCO3 from fluids if being used (see next slide)
    - Add sevalemer or alternative phosphate binder

Urine pH – a tricky game



- High urine pH (> 8.5)
  - GOOD for uric acid solubility (excreted without crystal formation)
  - BAD for Ca/Phos solubility (CaPhos crystals more likely)
- Low urine pH (< 6.5)
  - GOOD for Ca/Phos solubility
  - BAD for uric acid solubility

- If used at all, NaHCO3 is generally dropped once chemo starts (leukemic cells, particularly ALL cells, are high in phosphorous)
- Should be dropped at any point with concern for Ca/Phos crystals
- Consider following urine pH with each void to assess for risk

Hyper phos – how to treat

- Fluids – keep urine output high
- Phosphate binders – enterally
  - Sevelamer (renvela)
  - Aluminum hydroxide (amphogel) - can lead to aluminum toxicity
  - DON'T use Calcium Carbonate (fuel for crystals)
- Dialysis

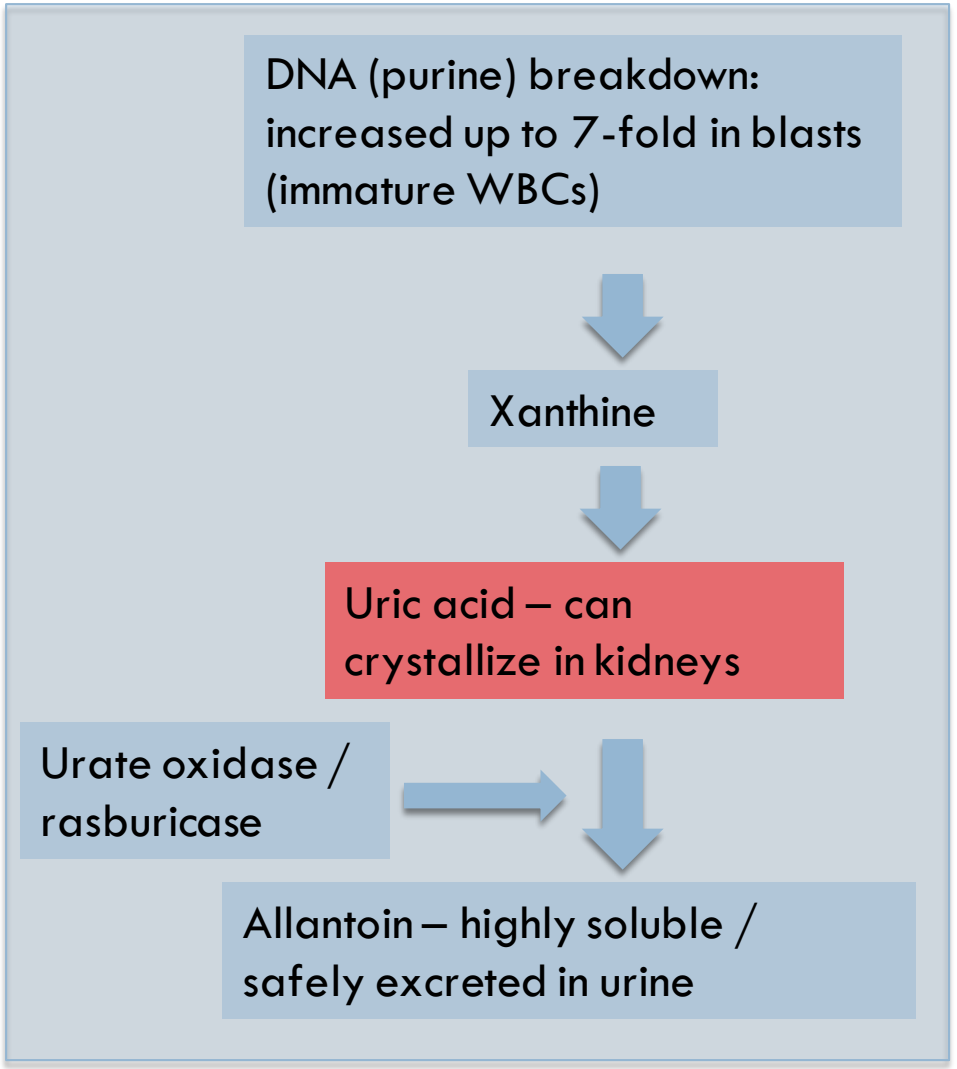
Case (cont)

- 36 hours into treatment. TLS labs comes back at 2am:
  - WBC 12 K
  - Uric acid 8.5 (nml 2-6), K 3.2, Phos 4.0 (3-5.5) Ca 8.5 (8.5-10.5) Cr 1.2

- *Any changes to medications?*

Uric acid management

- Urine - 4 to 6 ml/kg/hr
- Rasburicase (recombinant frog urate oxidase)
  - IV – given as a single dose
  - Draw uric acid on ice (otherwise enzyme keeps working on sample)
  - Stop alkalinized fluids
  - Causes hemolysis if G6PD (unknown status not a reason to hold up administration)
- What's the catch?
  - Expensive
  - Anaphylaxis
  - Increased liver function tests (LFTS)



REFERENCE SLIDES

Tumor Lysis Syndrome Case

IV fluids

- In general, we hydrate pediatric patients with
  - D5 (5% dextrose)
  - + ¼ or ½ 0.9% NaCl (Normal Saline or NS)
    - ¼ NS (38 mEq/L NaCl in 1 L) - hypotonic
    - ½ NS (77 mEq/L NaCl in 1 L) - isotonic
  - + 20 mEq/L KCl (potassium chloride) – avoided in patients with any concern for tumor lysis syndrome due to accumulation of potassium as cells lyse (potassium moves to extracellular environment)
  - Rate
    - Maintenance = 4/2/1 rule (4 ml/kg/hour for first 10 kg, 2 ml/kg/hr for next 10 kg, and 1 ml/kg/hr beyond 20 kg)
    - For example, the maintenance rate for a 24 kg patient would be:
      - 40 (for first 10 kg) + 20 (for next 10 kg) + 4 (for next 4 kg) = 64 ml/hr
      - 2x maintenance rate would be = 128 ml/hr

BACK TO CASE

REFERENCE MATERIAL

Tumor Lysis Syndrome Case

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CASE 3 – NAUSEA AND VOMITING

Location: Floor

- Nurse (RN) calling to ask for assistance with a patient experiencing increased nausea/vomiting
- Patient is a 5 year old male on day 2 of chemotherapy according to the center's high-risk brain tumor chemotherapy protocol including cylcophosphamide, cisplatin, vincristine, etoposide
- As part of his therapy, patient receives big doses of ondansetron (0.45 mg/kg) days 1-3 and IV dexamethasone (0.3 mg/kg) days 1-3 both every 24 hours to reduce nausea. No as needed (PRN) medications for nausea are prescribed.

- *Anything else you want to know? What would you like to do?*

History!

- Before assuming nausea is chemo related –
  - Make sure nausea is not related to other treatable medical condition
    - infection – urinary tract infection (UTI), gastroenteritis
    - obstruction/typhlitis/pancreatitis
    - intracranial pressure/shunt problem
    - Gastro-esophageal reflux (GER)
- Make sure the patient is hydrated

Patient history

- History – patient had tumor resection and placement of venticulo-peritoneal (VP) shunt at diagnosis (3 months ago)
  - Underwent radiation and first cycle without issue, other than e. coli UTI treated with ceftriaxone
  - Repeat brain MRI one month ago showed no residual tumor, no hydrocephalus
- According to RN and mom, patient has been a bit more sleepy today, but this is normal when he gets chemo. Seems to have more vomiting with this chemo.
- Ins/Outs (last 18 hours) - 1000/1200, urine output 3 cc/kg/hr.
- Last vital signs - HR 70, BP 135/85, RR 20
- Has not drank or eaten today, emesis x 4, multiple episodes of retching in last hour
- *Anything you are concerned about, in particular? What do you want to do at this point?*

Physical Exam

- Examine the patient!
  - Exam reassuring, patient able to cooperate with exam. Looks well hydrated. No dysuria.
  - Repeat vitals HR 100, BP 110/60, RR 20.

- Based on the exam, you are (appropriately) re-assured that the patient is well hydrated, and that the nausea is chemo-related.
- *Parents want to know – when is chemo-related nausea going to peak?*

Chemo – Emetogenic potential

- Potential for chemo-induced vomiting graded by chance of emesis – effects are additive
  - High (>90% chance of emesis) – cisplatin, high dose Ara-C (cytarabine)
  - Mod High – cyclophosphamide, ifosfamide, carboplatin, high dose methotrexate, idarubicin, dactinomycin
  - Mod (30-90%)– doxorubicin, daunorubicin, intrathecal (IT) cytarabine
  - Mod-Low – etoposide
  - Low – (10-30%)- vincristine, oral thiaguanine (TG), oral mercaptopurine (6-MP), corticosteroids
- This patient's regimen has very high emetogenic potential – hence the prophylactic high-dose ondansetron and dexamethasone - but break-through nausea is very possible.

Chemotherapy Induced Nausea/ Vomiting (CINV)

- Time course
  - Acute – within first 24 hours (usually 1-2 hours after chemo administration)
  - Delayed – greater than 24 hours (cisplatin has a second peak at 24-48 hours, can last 5 days)
  - Anticipatory – conditioned response to chemo
- Principles
  - Use scheduled anti-emetics when possible
  - Use what has worked for the patient before

Ondansetron (Zofran)

- 5-HT3 antagonist – extremely effective at preventing and treating acute CINV
- Dose (IV/by mouth (PO)/sub-lingual)
  - For highly emetogenic chemo – 0.45 mg/kg IV (max 24 mg) q 24 hours, ok to give one breakthrough dose (0.15 mg/kg) at 18 hours
  - Otherwise – dose is 0.15 mg/kg q 8 hours (0.1 mg/kg q 6 hours acceptable if patient prefers)
- Side effects – Headache, malaise/fatigue, constipation, increased liver function tests (LFTs)
- Considered a very safe and effective anti-emetic

Dexamethasone (Decadron)

- Dexamethasone - corticosteroid with great evidence to support its synergistic benefit to ondansetron
  - Meta-analysis showing it increased the chance of no acute vomiting by 25% (compared to ondansetron alone)
- Dosing:
  - Per chemotherapy protocol, consider 0.3 mg/kg IV daily
- In determining use, benefit is weighed against additional immunosuppression
  - Some centers avoid in conditions where dexamethasone is part of chemotherapy regimen (ALL, etc.)
- *Back to patient, he is not due for the breakthrough ondansetron dose – what can we do for his nausea?*

Case 3- continued

- Diphendydramine/metoclopramide
- A frequently used combination for chemotherapy-associated nausea and vomiting with good evidence of efficacy, generally well tolerated
  - Often used with oncology patients as second tier approach after ondansetron

Metoclopramide (reglan)

- Dopamine receptor antagonist
  - higher doses probably inhibit 5-HT3, has good evidence of anti-emetic effect, but with neurologic side effects
- Dosing
  - 0.5 mg/kg IV/PO q 4-6 hours; must always be given with diphenhydramine at this dose
- Side effects
  - Drowsiness, hypotension, diarrhea
  - **dystonic reactions** / **extra-pyramidal symptoms** (restlessness, agitation, spasms of neck/tongue/jaw – increased in children but not a contra-indication, but decreased with anti-histamine)

Diphenhydramine (benadryl)

- Anti-histamine
  - Not a true anti-emetic (effect is sedation) though often used as one with varying effect
- Dosing
  - 1 mg/kg (max 50 mg) IV/PO, no age minimum while inpatient, every 4-6 hours
- Side effects
  - sedation (not hypotension), may cause excitation – trial during daytime

Case 3 – Part 2

- After initial response to chemo, had local relapse requiring local radiation. Initially outpatient, but now being admitted due to increased nausea/vomiting
- On ondansetron, metoclopramide/diphenhydramine combination (staggered) as needed at home.

- *What else can you use for refractory nausea?*

Lorazepam (ativan)

- Benzodiazepine
  - Amnestic and anxiolytic properties, good for reduction of anticipatory nausea
  - Lower range of dosing decreases risk of hallucinations
- Dosing
  - Appropriate low dose is 0.03 mg/kg/dose IV/PO q 4-6 hours
- Side effects
  - sedation, respiratory suppression, hypotension. **Some evidence of increase in N/V in children <6 yo.**

Promethazine (phenergan)

- Antihistamine /anti-dopaminergic
  - Can cause dystonic reactions due to dopamine blockade – lessened with additional anti-histamine, sedation
- Dosing
  - 12.5 to 25 mg PO/IV q 4 to 6 hours
- **Cannot be used in children <2 years** (reports of death)

Scopalamine patch

- Anticholinergic – effective for prophylaxis for motion sickness
- Dosing – transdermal patch every 72 hours for patients age 10 and up
- Side effects – dry mouth, drowsiness, vision disturbance, urinary retention, dilated pupil if patient rubs patch then their eye
- Avoid use during radiation therapy

Dronabinal (marinol)

- Cannabinoid
  - Unclear benefit
    - not better than placebo to improve appetite, less efficacious than metoclopramide for chemo-related nausea
- Dosing
  - PO - 5 to 15 mg/m^2 every 4-6 hrs up to 6 doses/day (start at low dose less frequently to ensure tolerability)
  - Recommend using only in adolescent & young adults
- Side effects
  - vertigo, xerostomia, hypotension, dys- or euphoria, sedation

Case 3 – Part 2 (cont)

- Patient has less nausea, but has little appetite due to nausea. Patient is on:
  - ondansetron Q 8 hrs
  - diphenhydramine/metoclopramide Q 6 hrs
  - lorazepam Q 4 hrs
  - scopalamine patch Q 72 hrs

- *Any room for increasing? (What does a maxed out regimen look like?)*

What does a maxed out regimen look like?

- Ondansetron 0.15 mg/kg IV q 8 hours
- Staggering every 2 hours:
  - Diphenhydramine 1 mg/kg + Metoclopramide 0.5 mg/kg q 6 hours
  - Promethazine 1 mg/kg q 6 hours
  - Lorazepam 0.03 mg/kg q 6 hours
- Scopalamine patch
- Can also
  - Substitute prochlorperazine [compazine] (dopamine receptor antagonist) for metoclopramide 2.5 mg PO q 8-12 hours **(not in less than 2 year olds.)**
  - Drop one of the above agents if not tolerated and up another agents to q4

What's new?

- Aprepitant (Emend) – PO/IV
  - NK1 receptor antagonist
  - VERY efficacious for cisplatin containing regimen prevention and treatment of acute CINV
  - Side effects: Fatigue, Weakness, Hiccups, complicated metabolism – P450 effects
  - $$
- Polanosetron (Aloxi) – PO/IV
  - 2nd generation 5-HT3 receptor (40 fold increased affinity and longer half life than ondansetron – better for delayed emesis?)
  - Possibly more effective than ondansetron
  - Less of an improvement as combo with decadron
  - ? use in children
  - $$$

REFERENCE SLIDES

Nausea and Vomiting Case

Pediatric brain tumor chemotherapy

- Most pediatric brain tumors are treated with combinations of surgery (if amenable), radiation and chemotherapy in multiple stages of multi-agent regimen (induction and maintenance) usually over about a year
  - For infants (< 3 years), radiation therapy is avoided if possible to protect neurocognitive development
  - Pediatric brain tumors are generally considered higher risk if there are malignant cells found in the CSF (stage M1), metastastasis (stage M2-M4) or residual disease after surgery

BACK TO CASE

Shunt placement for brain tumors

- Most pediatric brain tumors are found in the posterior fossa and are frequently associated with obstructive hydrocephalus and elevated intracranial pressure (ICP) at the time of diagnosis
  - Signs of elevated ICP - vomiting, somnolence, Cushing's triad (hypertension, bradycardia, abnormal respirations)
- Shunt placement is delayed until surgical removal of brain tumor (if possible) as this often relieves the pressure
- If pressure concerns persist, ventriculo-peritoneal (VP) shunts are placed during or after the initial surgery to allow drainage of CSF during brain tumor therapy

BACK TO CASE

Normal vitals in children

age	Weight (kg)	HR	RR	Systolic blood pressure	Diastolic blood pressure
Newborn	3	100-160	30-60	50-70	29-45
6 mo	7	110-170	25-40	80-100	50-70
1-2 years	12	90-150	20-30	80-100	50-90
3-4 years	16	70-140	20-30	80-100	39-89
5-6 years	20	65-130	20-30	85-115	45-85
7-8 years	26	60-130	18-25	85-115	50-70
Adolescent	50	60-120	15-20	90-120	50-70

BACK TO CASE

REFERENCE MATERIAL

Nausea and Vomiting Case

Resources

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CASE 4 –
ACUTE CHEST SYNDROME

Location: Emergency Department

- 9-year-old female visiting from Morocco (arriving 2 weeks ago) presents to the ED with diffuse pain
- Per family she has been treated at a hospital in Morocco for multiple events per year that entailed pain and transfusion requirement, but the family was not aware of a diagnosis

Exam

- Exam - Temperature to 37.3, heart rate 97, respiratory rate 20, blood pressure 119/69, 99% on room air
- General: Sclerae are mildly icteric. Lungs: Clear bilaterally. Heart: Normal S1/S2, no murmurs. Spleen is palpable, non tender. Musculoskeletal exam: Global discomfort with range of motion of joints in all extremities. No local erythema or swelling of any joints.

- *What further tests would you like?*

Labs

- Complete blood count (CBC)
  - Hematocrit (hct) 21.3%, platelets (plt) 423, white blood count (wbc) 21.4 (81% polys, 1% bands)
  - Blood smear showing sickled cells
- Liver function tests (LFTs)
  - Bilirubin unconjugated 3.5, LDH 2300
- Sickle screen positive

- *Any other studies you want at this point?*

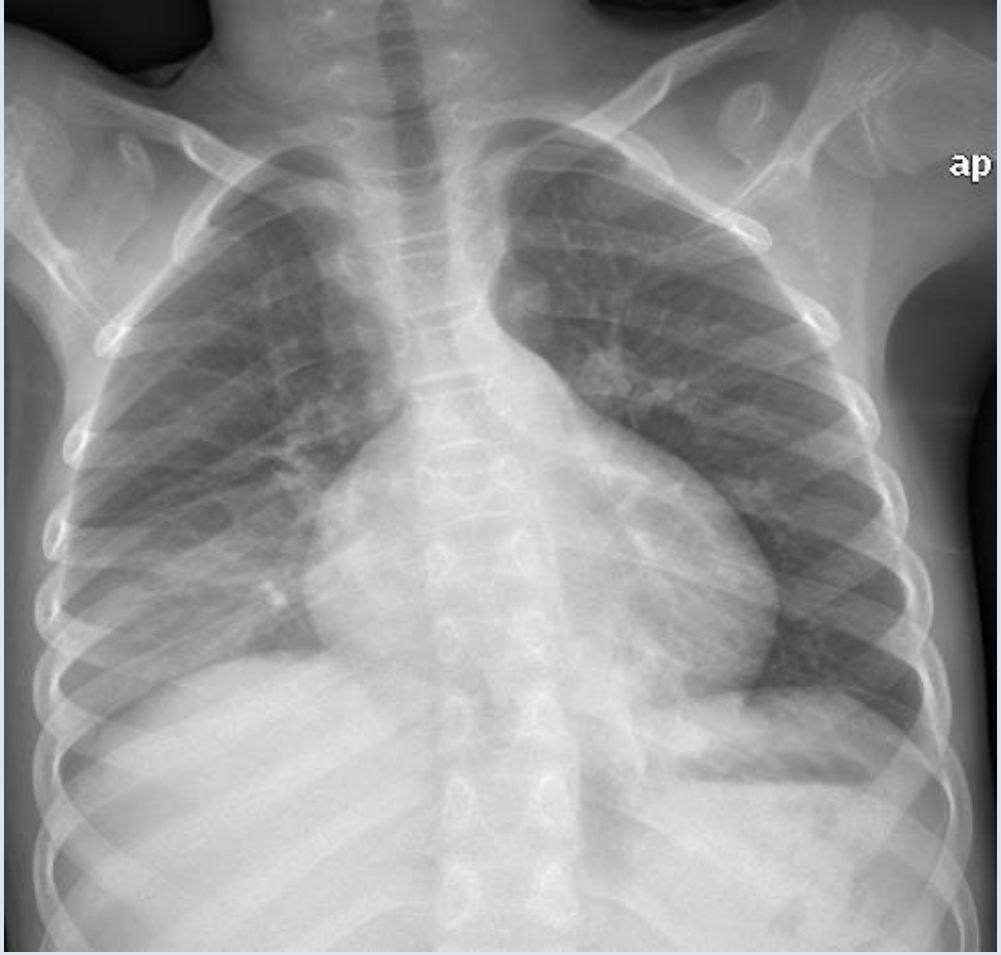
Additional sickle cell labs

- Reticulocyte count – sickle cell patients maintain their hematocrit with brisk red cell production; if this falls to "normal" or low levels during illness or stress, the baseline hemolysis will result in relative anemia
  - Raw reticulocyte count 11.7%
  - Hematocrit corrected reticulocyte count 6.6%
  - Reticulocyte production index 3.3%
- Ok to hold on blood culture (if afebrile and well-appearing) and chest x-ray for now (no respiratory symptoms)
- Formal electrophoresis to confirm diagnosis of sickle cell disease pending . . .

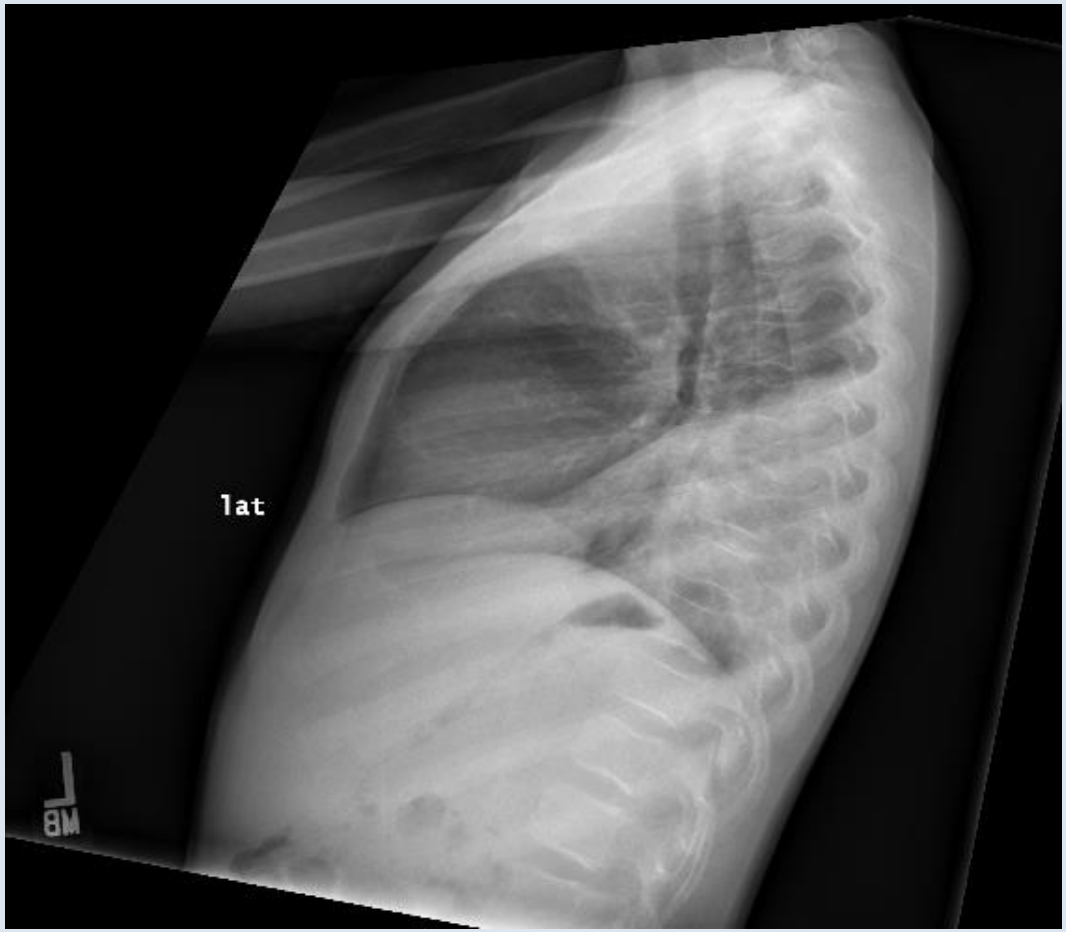
Case 4 – part 2

- RN calls to report that patient has new-onset tachypnea, low grade fever, oxygen saturation between 85% and 90%

- *Any interventions or studies at this point?*



Chest X-ray – anterior/posterior view



Chest X-ray – lateral view

Acute Chest Syndrome (ACS)

- A new (non-atelectatic) pulmonary infiltrate detected by chest radiograph in a sickle cell patient
  - Definition varies in different texts and at different institutions
    - some require lobar infiltrate and/or additional clinical findings (see next page)

Associated clinical findings

- These findings are occasionally (not always) present in some combination:
  - Chest pain
  - Temperature >38.5°C
  - Tachypnea, wheezing, cough, sputum production
  - Increased work of breathing (i.e., retractions)
  - Hypoxemia relative to baseline measurements

ACS – Epidemiology / Management

- Epidemiology:
  - Most common in:
    - Younger children (more susceptible to infection?)
    - Hemoglobin SS genotype /Sickle beta zero (S-B0) thalassemia
  - High fetal hemoglobin (HbF) protective
  - Higher leukocyte count correlates with higher mortality with acute chest episode
- Management:
  - Goal is to improve factors leading to deoxygenation of HbS and injury to lung tissue
  - *What are these factors?*

Improving oxygenation in ACS

1. Hydration
2. Infection
3. Pulmonary
4. Pain
5. Anemia
6. Inflammation

1. Hydration

- *What is the GOAL?*
  - Euvolemia! OK to be active to maintain this, but use gentle steps and re-assess
    - Dehydrated - gentle boluses of IV fluids (10 ml/kg at a time)
    - Fluid overloaded – diuretic (furosemide)
    - If roughly euvolemic – DO NOTHING, start IV fluids at a rate of:
      - PO (oral intake) + IVF = maintenance

2. Infection

- *What labs/what antibiotics?*
  - Labs: blood culture, other labs with symptoms
  - Antibiotics: Ceftriaxone and azithromycin (for atypical bacteria such as mycoplasma pneumonia)
    - And vancomycin if very ill-appearing for coverage of resistant gram positives

- *Medical student asks whether acute chest is caused by infection or vaso-occlusion. . .*

Pathophysiology

- Could be one or more of any of the following (will not be able to differentiate based on clinical appearance/radiograph):
  - Infection (viral, bacterial, atypical)
  - Vaso-occlusive
  - Ischemic/hemorrhagic
  - Embolic
  - Edema
  - Hypoventilation

3. Pulmonary

- *What tools do you have?*
  - Oxygen – Maintain oxygen saturation > 92% (> 94% at some centers)
  - Albuterol – very low threshold to start, continue with any evidence of airway reactivity or improvement after treatments
  - Incentive spirometry – q 2 hours, avoid hypoventilation/atelectasis
  - Avoid inactivity/oversedation leading to hypoventilation

4. Pain

- Under-treating pain is a bigger problem than over-treating pain – stay ahead of the pain to allow patient to breath more deeply and comfortably
- Ketorolac – [better analgesia] up to 3 to 5 days
  - OR ibuprofen [better anti-inflammatory]
- Morphine –
  - low threshold to start patient-controlled analgesia (PCA) – can use lower narcotic doses overall by keeping on top of pain
  - Consider nalbuphine

Case 4 – part 3

- Patient is clinically stable – on room air and antibiotics. Follow-up CBC comes back at 6 am.
  - Hct 17%, retic 12%

- *Any intervention you want?*

6. Anemia – transfusion

- Theoretic benefit (increased oxygen carrying capacity, less proportional HbS)
  - Simple transfusion; Partial exchange transfusion
  - Cochrane's review (Alhashimi D et al. 2010): no clear evidence to support transfusion
- Concerns
  - Alloimmunization/delayed hemolytic transfusion reaction/hyperhemolysis (DHTR/H), seen in 5% to 35% of transfused sickle cell patients (Talano J. et al. *Pediatrics*. 2003.)
  - Increased with ethnic/antigen mismatch between donor/recipient
- Indications for simple transfusion vary at different institutions
  - Contraindications to consider include high hematocrit/hemoglobin (e.g., Hct >25%/Hgb > 9), or concerns for fluid overload
- Consider exchange transfusion if continued decline despite simple transfusion (with at least a day to assess for response)
  - Can lead to fluid shifts and hemodynamic instability

6. Inflammation – steroids

- Potential benefit in mild/moderate ACS
- Largest retrospective study
  - Steroid use resulted in longer hosp stay and higher re-admission rate
- May be beneficial with patients with documented asthma – should wean after steroid course to prevent "rebound ACS"

REFERENCE SLIDES

Acute Chest Syndrome Case

Sickle cell screen

- Hemoglobin S (HbS) Solubility test – tests for presence of HbS by looking for sickling with reduced oxygen availability
  - Screening test - not sensitive or specific
  - Doesn't distinguish trait from disease
  - Diagnosis needs to be confirmed with electrophoresis

BACK TO CASE

Fetal hemoglobin (HbF)

- Oxygen is carried in red blood cells by hemoglobin – a tetramer made of two alpha and two beta chains
- Fetal hemoglobin (HbF) is the main form in late fetal circulation, and has two gamma chains instead of beta chains (where the sickle mutation is found)
- Persistence of HbF in sickle cell patients provides non-sickling RBCs and helps with oxygen delivery
- HbF production is increased with hydroxyurea

BACK TO CASE

IV fluids

- In general, we hydrate pediatric patients with
  - D5 (5% dextrose)
  - + ¼ or ½ 0.9% NaCl (Normal Saline or NS)
    - ¼ NS (38 mEq NaCl in 1 L) - hypotonic
    - ½ NS (77 mEq NaCl in 1 L) - isotonic
  - + 20 mEQ KCl (potassium chloride)
  - Rate
    - Maintenance = 4/2/1 rule (4 ml/kg/hour for first 10 kg, 2 ml/kg/hr for next 10 kg, and 1 ml/kg/hr beyond 20 kg)
    - For example, the maintenance rate for a 24 kg patient would be:
      - 40 (for first 10 kg) + 20 (for next 10 kg) + 4 (for next 4 kg) = 64 ml/hr
      - 2x maintenance rate would be = 128 ml/hr

BACK TO CASE

Reticulocyte count

- Reticulocytes are immature red blood cells (RBCs) that normally comprise about 1% of circulating RBCs. They have "reticular" RNA that is detectable with certain dyes.
- They are used as a marker of marrow production of RBCs, because their presence indicates recently-produced cells.
- The **raw reticulocyte count** is the percentage of RBCs on a peripheral smear that are reticulocytes (reticulocytes/total red blood cells)
  - 0.5% to 1.5% is an expected range in a non-anemic patient
- Calculated indices to evaluate response to anemia:
  - The **hematocrit-corrected reticulocyte count** is corrected for the degree of anemia [reticulocyte count x (measured hematocrit/expected hematocrit)]
  - The **reticulocyte production index (RPI)** is the hematocrit-corrected reticulocyte count (see above) multiplied by the maturation index – a formula to correct for the longer life span of reticulocytes using a standardized table
    - No "normal range," but RPI > 2 is usually consistent with brisk marrow production of red blood cells

BACK TO CASE

REFERENCE MATERIAL

Acute Chest Syndrome Case

Resources

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