Pediatric oncology Emergency

Learning Objective:

1-To know the most important pediatric oncology emergency

2-How you deal with this condition

3-As this lifethreating condition you should take action immediately

Tumor lysis syndrome(TLS)

- Severe metabolic abnormalities associated with the onset of therapy particularly in the setting of lymphoma and leukemic can have high morbidity and mortality.
- Occur as a result of spontaneous or treatment related breakdown of tumor cells release of intracellular contents from the tumor cells into the blood stream hyperuricemia hyperkalemia and hyperphosphatemia

Risk factor (TLS)

- Presence of bulky disease.
- Adenopathy, hepatosplenomegaly and high leukocyte count.
- ↑ lactate dehydrogenease, uric acid creatinine, and decreased urine output.
- TLS is highest at 12-72 hr after initiating chemotherapy.
- Symptom can also precede the therapy or occur as long as 7 days later.
- The main principle of TLS prevention and treatment.

Pathophysiology

- It can occur spontaneously prior to the administration of chemotherapy or follows the initiation of therapy.
- In tumors with a high proliferative rate, large tumor burden and high chemo sensitivity.
- Massive cell lysis, with the release of intracellular anions- cat ions and breakdown produced of nucleic acid and proteins into the bloodstream.
- Hyperuricemia is the most common finding due to release of intracellular nucleic acids and subsequent catablison of the purine nucleotides, adenosine and guanosine .
- Uric acid the final product of both endogenous and dietary purine nucleotide catabolism generate in the liver by oxidation of xanthine to uric acid by xanthine oxidant.
- Hyperkalemia - kidney inability to excrete the massive quantities of intracellular potassium .
- Hyperphosphatemia result from rapid release of intracellular phosphorus from tumor cells nephrocalcinosis - renal failure.
- Normal calcium and phosphorus ranger between 30 and 55 mg^2/dL^2 where this exceeds 70mg^2/dL^2 calcium phosphate dispositive in the kidney.

Incidence

The higher incidence of TLS occur in :

- Acute lymphoblastic leukemia (5.2%)
- High grade non –Hodgkin's lymph (6.1%).
- B-cell acute lymphoblastic.
- Acute myeloid leukemia .
- Chronic lymphoblastic leukemia
- Multiple myeloma
- Chronic myeloid leukemia in blast crisis.
- Hodgkin's disease
- Solid tumors that are highly chemo sensitive or that have high tumor burden,
- bulky metastatic disease or tumors that have present with renal compromise.
- Tumors with higher response to cytotoxic therapy such

Diagnosis of TLS

Tow classification systems for TLS have been developed

1- Hande – Garrow Definition of laboratory tumor lysis syndrome (L TLS)

- L TLS: 25% increase over pretreatment values in serum phosphate, potassium, uric acid or urea nitrogen.
- Or -25% decline in serum calcium.
- (Any two of the above metabolic changes must occur within 4 days of treatment).

2- Hande –Garrow definition of clinical tumor lysis syndrome (C TLS).

- Rise in serum creatinine > 2-5mg /dL.
- Serum K level > 6.0mmol /L.
- Decline is serum calcium to < 6mg/dL.
- Development of life threatening arrhythmia or renal insufficient, cardiac arrhythmias, sudden death and seizures.

(TLS is defined as the presence of laboratory tumor lysis syndrome and any one of the above criteria) .

Clinical manifestations of TLS and treatment

- Nausea, anorexia.
- Cardiac arrhythmia .
- Seizures .
- Muscle cramps, tetany.
- Oliguria or anuria.
- Alterations in consciousness

Management of patients at risk for TLS

- **Fluids and Alkalization :-**

- Aggressive hydration 3000ml/m2/day (1/2 G.S).
- Urine output should be maintained more than 100ml/m2/hr – urine s.q ≤ 1.010.
- Diuretics may be used (mannitol 0.5g/a) furosemide 0.5-1 mg//g.
- Urine alkalization (urine PH ≥ 6.5-7.5 / sod. Bica.40 mg/m2.

- **Hyperkalemia (serum K≥ 6.0mm/L**

Neuromuscular sign and symptoms muscle weakness, cramps, and paresthesia. Cardiac manifestations may include peak T-wares, malignant arrhythmias and conduction disturbances

Hyperuricemia

- Serum uric acid ≥ 8.0mg/ or 25% ↑from baseline 3 day before or 7 day.
- Intraluminal renal tubular ,acute renal dysfunction.
- Management of hyperuricemia are allopurinol and rasburicase.
- Allopurinol oral or iv…. 100mg/m2 every 8hr, 200-400 mg/m2/day.

- Recombinant form of urate oxidase (rasburicase 0.15-0.20mg/kg IV for 5-7 days. ↓ uric acid level by 4 hours after treatment.

Uremia and Acute Renal failure

causes

- Uric acid crystal obst. uropathy.
- Renal precipitation of calcium phosphate.
- Xanthinuria.
- Nephrotoxic drugs.
- Intravscular volume depletion.

Treatment

- Hemodialysis or Continuous hemofiltration

Hyper leukocytosis and leukostasis

Is life threatening pediatric oncologic emergency that requires immediate initiate of appropriate therapy.

Definition

Hyperleukocytosis is generally accepted as a (WBC) count higher than 100x10`/L or higher than 50x10`/L ..most frequent occur in:

- Infant acute lymphoblastic leukemia.
- T- cell ALL.
- Subtypes of ALL.
- Acute myeloblastic leukemia(AML) & Chronic myeloblastic leukemia(CML)

Leukostasis

Stasis of leukemia cells within blood vessels and migration of blast cells into tissues can lead to the clinical entity of leukostasis

1. Most frequently in AML. (M4-M5) subtypes.
2. Clinical symptoms from leukocytosis occur at (WBC) higher than 200-300 x10`/L ALL.
3. Leukostasis have been observed in patients with WBC 100x10`/L

Clinical symptoms of leukostasis

- Depend on the system affected
- Any small vessels, any organs could be affected
- Hyperleukocytosis leads to leukostasis
- Symptoms may be caused by release of intracellular components of blast cells after lysis including enzymes → injury in surrounding tissue → aleveolar damage and interstitial .
- Leucostasis → renal failure, , dactylitis, priapism and clitorism, acute myocardial infarction and cardiac failure .
- May be Asymptomatic
- Clinical leukostasis can present subtly and evolve rapidly.
- Pulmonary symptoms: tachypnea, oxygen desaturation, dyspnea and progress rapidly to acute respiratory disease syndrome (ARDS) and Resp. failure.
- Neurologic symptoms: headache, papilledeme tinnitus, ataxia, behavioral changes, seizures and stroke.
- Hemorrhagic stroke in a highly morbid complication of hyperleukocytosis → Microgranular variant of M3 AML (M3v).

Treatment of hyperleucocytosis

- Hydration, urinary alkalinization and Allopurinol
- Urate oxalate decrease the risk for TLS
- Cranial radiation to decrease the chance of intracerebral hg. (400 to 600 rad)
- The use of low dose prednisone.
- Exchange transfusion.
- Leukapheresis (Pt wt < 12kg unable to undergo leukapheresis) → 50-60% is WBC) (ALL-AML but no APML → ↑ hg)
- Hydroxyurea.

Febrile Neutropenia (FN)

- Common and dangerous consequence of myelosuppressive chemotherapy but can occur as part of the disease processes.
- Bacterial blood stream infection is the most commonly diagnosed cause, commonly Gram-positive.
- Gram-negative organisms are becoming more prevalent,
- When FN is prolonged, lasting for more than 5 days, there is an increased risk of invasive fungal infections.

Febrile neutropenia Defines as a temperature ≥38°C with an absolute neutrophil count (ANC) of less than 500 cells/microlitre

The course of an episode of FN
depends upon the length of neutropenia and fever. Some patients will recover within 24–48 h of commencing broad spectrum antibiotic treatment. Prolonged FN (greater than 5 days) is associated with fungal infections,
Children who do not have a documented infection 48 h after initial blood cultures were taken, who have been afebrile for more than 24 hr who are clinically stable and whose neutrophils are recovering can either be stepped down to oral antibiotics or antibiotics may be stopped altogether

Neutropenia classified to

- Mild neutropenia (ANC1000 - < 1500): minimal risk of infection
- Moderate neutropenia (ANC 500 - < 1000): moderate risk of infection
- Severe neutropenia (ANC < 500): severe risk of infection.

$$ANC = \frac{(\%neutrophils + \%bands)\times(WBC)}{(100)}$$

Note : ANC means Absolute neutrophil count

Diagnosis of FN

- History
- Examination :
- Vital signs (temp, RR, blood pressure,HR) and assessment for haemodynamic instability.
- A rectal temperature should not be measured in oncology patients because compromised rectal mucosal integrity can induce a Gram-negative bacteraemia even with mild trauma.
- Skin signs of cellulitis, abscess or impending skin integrity breakdown, including around the central venous line (if present), perineum and labial skin folds.
- Examination of the mouth for mucositis or gingivitis.
- Examine the ears, nose and throat for signs of upper respiratory tract infection, otitis media and sinusitis.
- A careful respiratory examination. Subtler signs of infection may include just an elevated respiratory rate.
- Listen to the heart sounds.
- An abdominal examination,also Check for new hepatosplenomegaly and perianal area examination including looking for anal fissure or infection .

Workup for FN patient

- Complete blood cell count (CBC)+ Blood film
- Blood cultures (at least two sets with a set collected simultaneously from each lumen of an existing central venous catheter if present, and from a peripheral vein)
- Serum creatinine and blood urea nitrogen and Electrolytes
- Cultures from suspected infection sites (eg, urine, lower respiratory tract, CSF, stool, wounds)
- LFT
- consider a blood gas
- Chest X-Ray for patients with clinical manifestations of lower respiratory tract infection OR CT chest IF no findings
- Patients with a flulike illness should have a nasopharyngeal swab
- Abdominal ultrasound can be considered after 72 h of fever, to assess whether there is fungal involvement of the kidney and/or liver
- Bone marrow aspiration and biopsy
- Swabs of any inflamed or discharging skin or mucous membrane sites, should be send for microscopy and culture.
- (PCR) on blood, respiratory secretions, or other bodily fluids (apart from urine) can allow for faster diagnosis and more targeted antimicrobial therapy which may be of shorter duration.

Treatment of FN

Oncology patients are considered at lower risk of septic complications unless one or more of the following conditions apply:

- treatment for AML or Burkitt lymphoma, induction phase of ALL
- progressive disease; or relapsed disease with marrow involvement
- presenting with any of the following features:
    - hypotension
    - tachypnoea
    - hypoxia—defined as saturations less than 94% in air
    - new changes on CXR
    - altered mental status
    - severe mucositis
    - vomiting or abdominal pain
    - focal infection
    - neutrophil count less than 0.1×10^{9} /L
    - Kidney or liver insufficiency

➢ **Any patients deemed to be high-risk should be treated as an inpatient**

Empiric treatment of FN

First line treatment of FN is with broad spectrum antibiotics ensuring coverage of both Gram-positive and Gram-negative organisms.

❑ For low-risk patients

1- Oral antibiotic therapy in (outpatients and select inpatients)

- Ciprofloxacin plus amoxicillin/clavulanate . clindamycin may be substituted for amoxiclilin in penicillin-allergic patients
- Moxifloxacin if *Pseudomonas* coverage is not required

2. Or i.v Monotherapy includes :(one of the following treatment)

- Beta-lactam antibiotics, e.g. piperacillin-tazobactam, if anaphylaxis to penicillin, then ciprofloxacin plus a glycopeptide such as vancomycin or teicoplanin.
- Cefepime

- Meropenem
- Imipenem-cilastatin

❑ For high risk patient urgent treatment in the hospital with aggressive management needed

Tailoring antibiotics

- Patients with a microorganism confirmed infection should have their antimicrobial therapy tailored to the particular infection and antibiotic sensitivities, with duration of 7–14 days usually appropriate depending upon the organism (longer courses for Gram-negative organisms) and neutrophil count (antimicrobials are often continued until the neutrophil count is consistently increasing).
- Any patient with new clinical instability or worsening of symptoms should be urgently re-assessed with consideration of reinvestigation and escalation of treatment.
- Colony stimulating factors such as GCSF be considered in severe prolonged neutropenia without anticipated bone marrow recovery and significant sepsis

Suspected fungal infection

Patients who have been febrile for more than 72–96 h on antimicrobial therapy, especially those with negative blood cultures, should be investigated for fungal infection and commenced on an antifungal treatment.
The most common first line antifungal drug is liposomal amphotericin B