Oncologic emergencies

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Objectives

- 1. ให้การวินิจฉัยภาวะ metabolic emergencies ที่พบบ่อยในผู้ป่วยมะเร็งเด็ก รวมถึงแนวทางการรักษาที่ถูกต้องเหมาะสม
- 2. ให้การวินิจฉัยและวินิจฉัยแยกโรคในภาวะ superior venacava syndrome รวมถึงแนวทางการรักษาที่ถูกต้องเหมาะสม
- 3. ให้การวินิจฉัยภาวะ Typhlitis รวมถึงแนวทางการรักษาที่ถูกต้องเหมาะสม
- 4. ให้การวินิจฉัยภาวะ febrile neutropenia รวมถึงแนวทางการรักษาที่ถูกต้องเหมาะสม

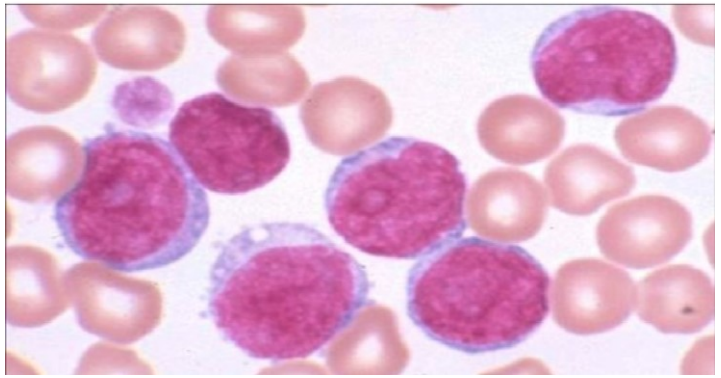
Outlines

- Hyperleukocytosis
- Tumor lysis syndrome
- SVC syndrome
- Typhlitis
- Febrile neutropenia

Hyperleukocytosis

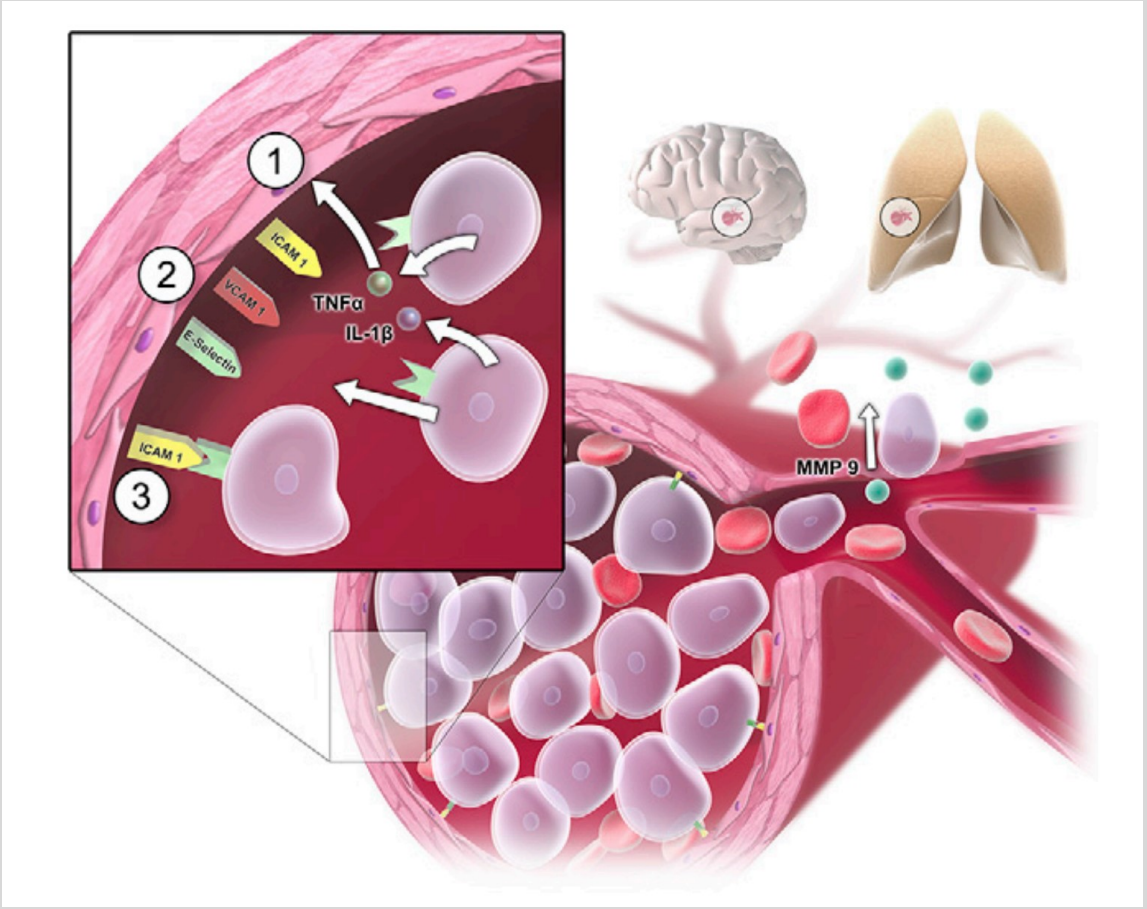
Case scenario

- A 10 year-old-boy presented with low grade fever for 2 wks. He had bleeding per gums and ecchymosis. Today, he become dyspnea.
- PE: moderately pale, no jaundice, 2-3 cm anterior/posterior cervical lymph nodes, 2/6 systolic murmur at LPSB, Hepatosplenomegaly, liver 3 cm BRCM spleen 4 cm BLCM
- CBC: Hb 7 g/dl, Hct 22 % , WBC 530,000 /mm^3, plt 25,000 /mm^3 , Blast 90%, Lym 10%
- **What should we do next?**



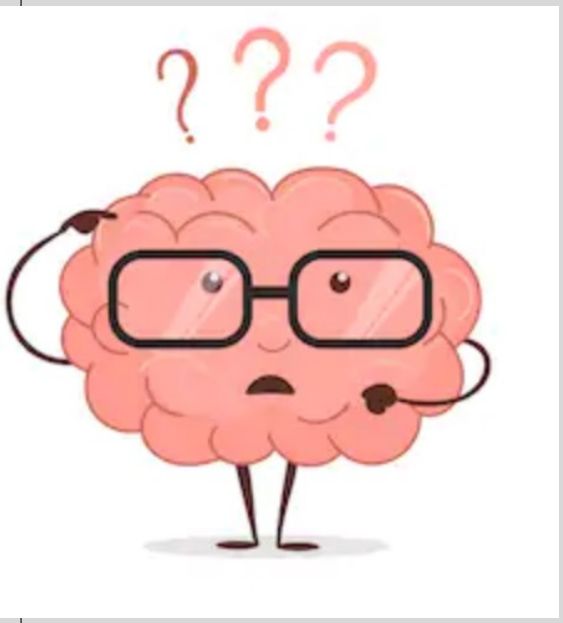
Hyperleukocytosis

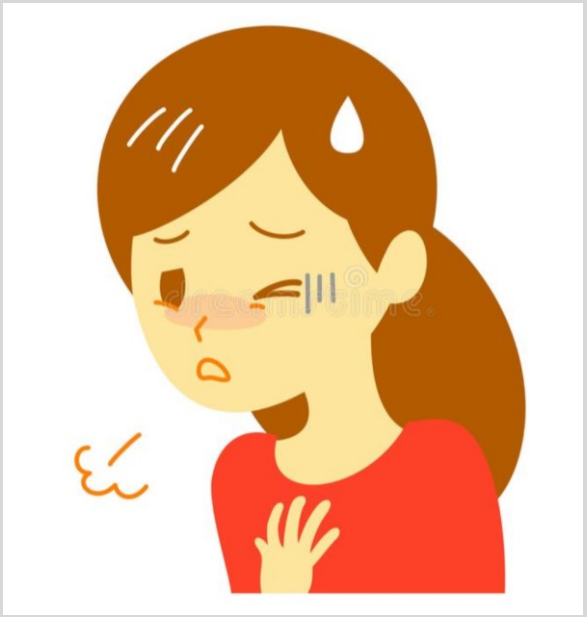
- Total white cell count > **100,000/mm^3**
- **Adhesive reaction with endothelium And sludging**
- **Cytokine production**
- **Results: Tissue hypoxia, microthrombi and secondary hemorrhage**



Rollig et al, Blood 2015

Leukostasis : clinical symptoms





Management

- **Aggressive hydration** 3-4 L/m^2/day to keep urine output > 3 ml/kg/hr
- **Leukocyte reduction**
  - Leukapheresis or exchange transfusion
  - Indication
    - Symptomatic patient
    - Asymptomatic :

      AML :WBC >200,000/mm^3

      ALL, CML :WBC >300,000/mm^3
  - Contraindication in APL

Management

- **Transfusion**

  Platelet transfusion : keep platelet >20,000/mm^3 (decrease risk ICH)

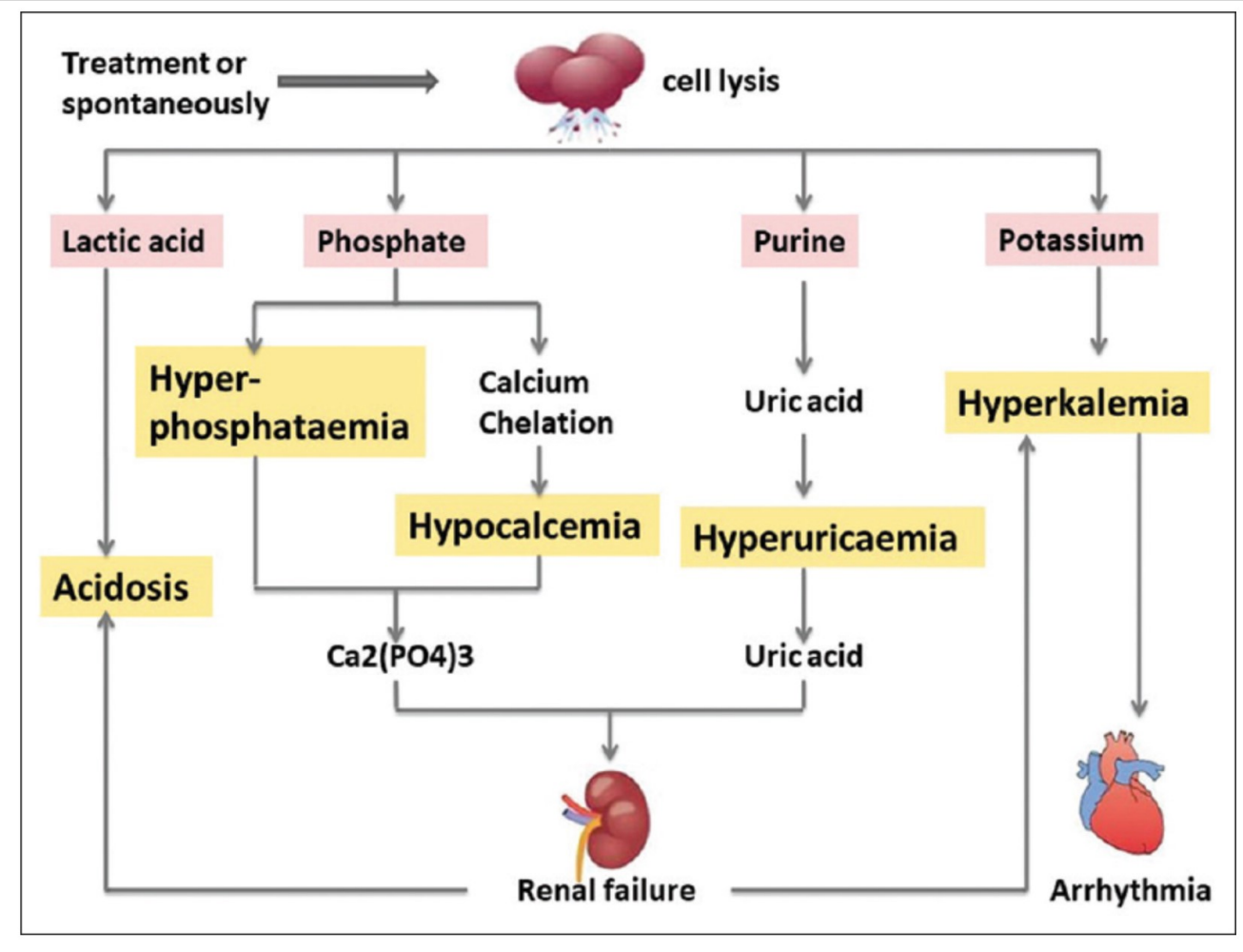
  FFP and vitamin K : coagulopathy prior to any invasive procedures

  RBC transfusions : should be avoided ✖

- **Chemotherapy :** early start

Tumor lysis syndrome

Pathophysiology



Criteria for diagnosis

Laboratory tumor lysis syndrome	
Uric acid	ระดับในเลือด ≥ 8 mg/dl หรือมีค่าสูงขึ้นจากระดับตั้งต้น ≥ 25%
Potassium	ระดับในเลือด ≥ 6 meq/L หรือมีค่าสูงขึ้นจากระดับตั้งต้น ≥ 25%
Phosphate	ระดับในเลือด ≥ 6.5 mg/dl หรือมีค่าสูงขึ้นจากระดับตั้งต้น ≥ 25%
Calcium	ระดับในเลือด ≤ 7 mg/dl หรือมีค่าต่ำลงจากระดับตั้งต้น ≥ 25%

Clinical tumor lysis syndrome

1. **ค่า Creatinine ในเลือด ≥ 1.5 เท่าของค่าปกติสูงสุดตามช่วงอายุ**
2. **หัวใจเต้นผิดจังหวะ หรือ เสียชีวิตเฉียบพลัน**
3. **มีอาการชัก**

Risk factors of tumor lysis syndrome

Characteristic	Risk Factor
Tumor type	Burkitt's lymphoma Lymphoblastic lymphoma Diffuse large-cell lymphoma ALL Solid tumors with high proliferative rates and rapid response to therapy
Tumor burden/extent of disease	Bulky disease (>10 cm) Elevated LDH (> 2× ULN) Elevated WBC (>25,000/μL)
Renal function	Preexisting renal failure Oliguria
Baseline uric acid	Baseline serum/plasma uric acid > 450 μmol/L (7.5 mg/dL)
Effective and rapid cytoreductive therapy	Disease-specific therapy, varies according to tumor type

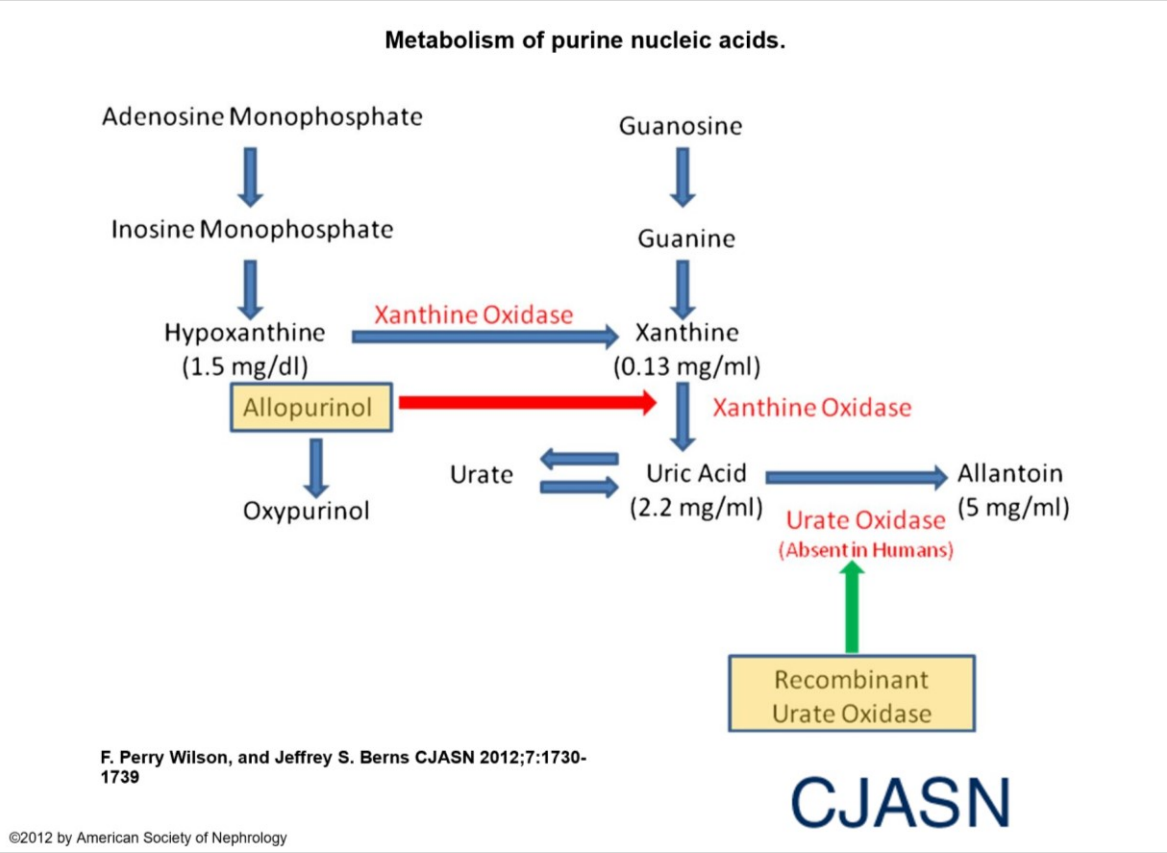
Abbreviations: ALL, acute lymphoblastic leukemia; LDH, lactate dehydrogenase.

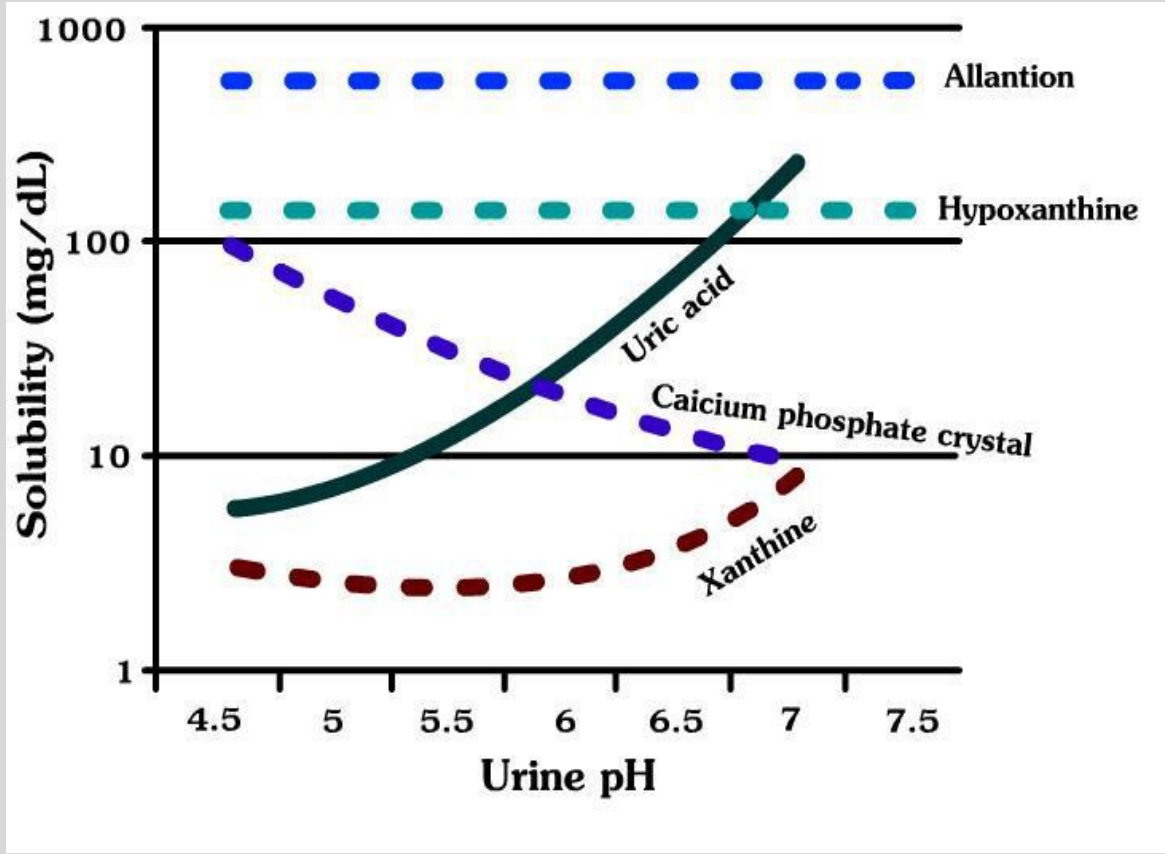
Coiffier B et al., 2008

Management

1. Aggressive hydration → **3-4 L/m^2/day**, start 24 hr before chemotherapy
2. Diuresis → Furosemide/mannitol, keep urine output **> 3 ml/kg/hr**
3. Electrolyte management
4. Leukocyte reduction
5. Dialysis
6. Monitoring

Electrolyte management





Pui CH. Childhood Leukemia. 2006.

Electrolyte management

Potassium

K < 6 meq/L with asymptomatic

- Hydration and diuretics
- Kayexelate or kalimate : dose of 1 g/kg every 6 hr

Moderate to severe hyperkalemia

- EKG
- RI 0.1 U/kg/hr plus 50%glucose 0.5 g/kg/h
- IV calcium gluconate 1-2 ml/kg
- NaHCO3 1-2 meq/kg IV

Phosphate

- Aluminum hydroxide 150 mg/kg/day every 4-6 hr
- Hydration
- Dialysis

Calcium

- Ca x Po4 > 60 ➔ renal calcification
- 10 mg/kg of elemental calcium: for symptomatic hypocalcemia

Electrolyte management

Leukocyte reduction and specific CMT

Dialysis

progressive renal failure with

potassium > 6 mEq/l

phosphate >10 mg/dl

oliguria, anuria

volume overload

Monitoring

Electrolytes; calcium, phosphorus, potassium, uric acid, BUN, and creatinine every 4-12 hr

Management

1. Aggressive hydration → **3-4 L/m^2/day**, start 24 hr before chemotherapy
2. Diuresis → Furosemide/mannitol, keep urine output **> 3 ml/kg/hr**
3. Electrolyte management
4. Leukocyte reduction
5. Dialysis
6. Monitoring

Back to case scenario

Start IV fluid at 3L/m^2, no Potassium

Low Potassium, Phosphate diet

Check other labs : BUN, Cr, Electrolytes, Uric acid, LDH , DIC panel, PT, PTT, INR

Type and cross blood and platelets

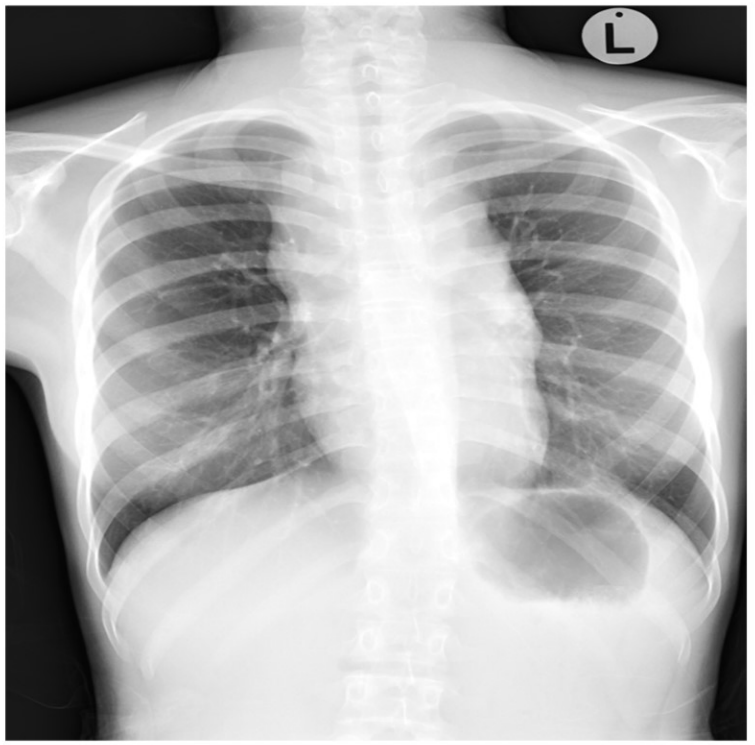
Get a Chest X-ray : Rule out mediastinal masses.

Prepare for leucocyte reduction (total blood exchange/ leukapharesis)

SUPERIOR VENA CAVA SYNDROME

Case scenario

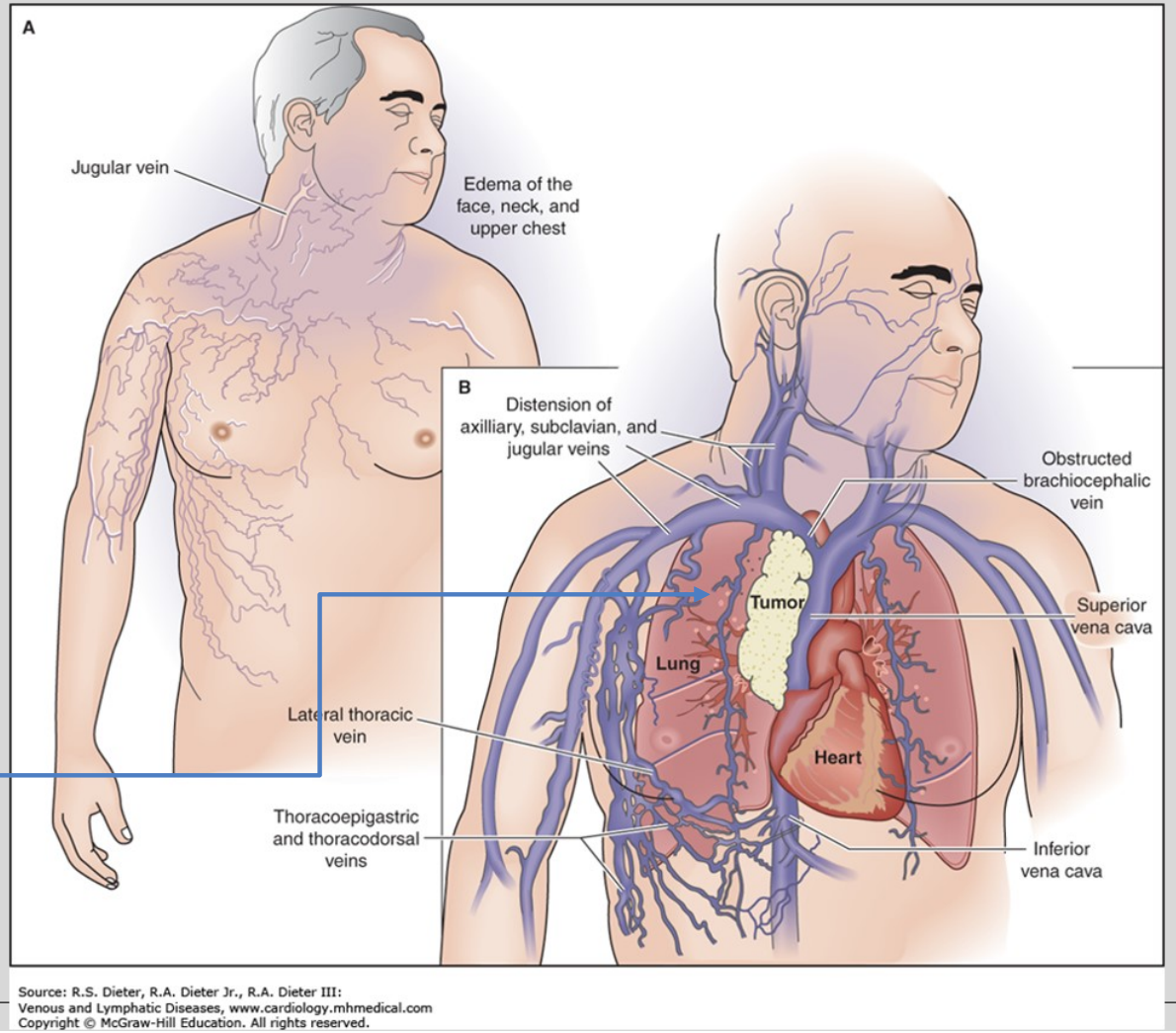
- A 12-year-old girl presents with facial swelling. Physical examination reveal BT 37°C, PR 100 beats/min, RR 22 breaths/min, BP 100/70 mmHg, facial swelling, conjunctival suffusion, not pale, no jaundice, distention of the jugular veins and superficial veins at upper chest, palpable bilateral cervical lymph node 1 cm and right supraclavicular 1.5 cm, impalpable liver and spleen,
- Tumor marker: LDH 400 U/L
- **Which is the most appropriate management in this patient?**



Superior vena cava syndrome

- Superior vena cava syndrome (SVCS)
  - signs and symptoms of superior vena cava (SVC) obstruction due to compression or thrombosis
- Superior mediastinal syndrome (SMS)
  - SVCS + tracheal compression

Anterior mediastinal tumors
a. Hodgkin lymphoma.
b. Non-Hodgkin lymphoma.
c. Teratoma or other germ cell tumor.
d. Thyroid cancer.
e. Thymoma.



Source: R.S. Dieter, R.A. Dieter Jr., R.A. Dieter III: Venous and Lymphatic Diseases, www.cardiology.mhmedical.com

Supportive treatment

1. Avoid supine position
2. Avoid Stress, Sedation
3. Avoid intravenous access at arms
4. Diagnosis should be made quickly

   a. Radiograph of the chest and CT

   b. Screening blood work such as CBC, LDH, uric acid, AFP, and β-hCG

   c. Tissue biopsy

Specific treatment

Malignancy cause

1. **Empirical treatment.**
    - **Radiation**
    - **Steroids (tx hematologic malignancies, decrease airway edema)**
2. **Biopsy mass when patient is stable.**
3. **Specific chemotherapy after biopsy**

Vascular thrombotic cause

Anticoagulation for symptomatic venous thrombosis (Heparin or LMWH)

Typhlitis

Typhlitis

necrotizing colitis

often localized in the **cecum**

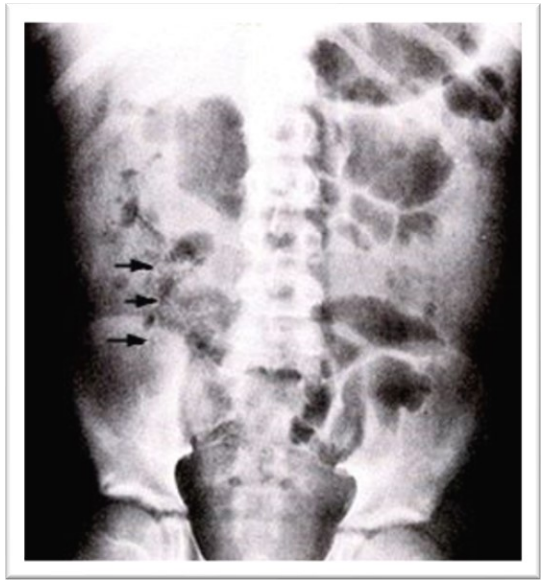
occurs in the setting of severe neutropenia

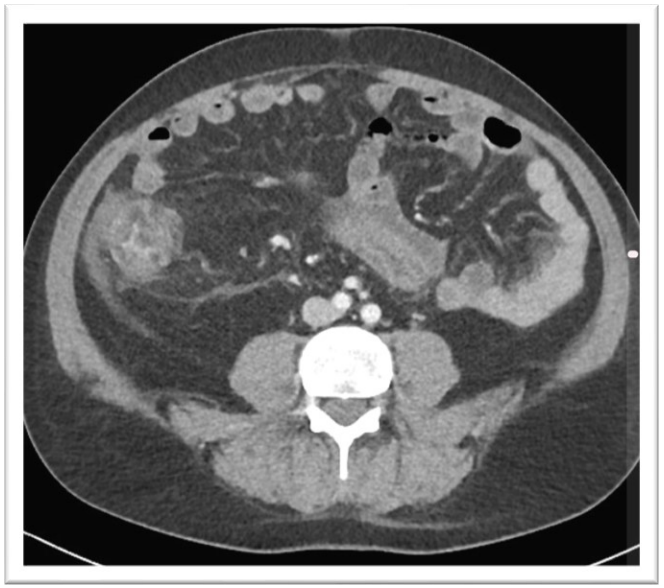
Etiology

1. Pathogens : **Pseudomonas species, Escherichia coli, other Gram-negative bacteria**, Staphylococcus aureus, α-hemolytic Streptococcus, Clostridium, Aspergillus, and Candida.
2. Cytotoxic chemotherapeutic agents → mucosal injury

Diagnosis

Clinical findings : Right lower quadrant pain, absence of bowel sounds, bowel distention, palpable mass in the RLQ





https://radiopaedia.org

www. Uptodate.com

Treatment

- Discontinuation of oral intake.
- Nasogastric tube to suction.
- Broad-spectrum antibiotics (anaerobic and Gram-negative coverage)
- Intravenous fluid, electrolytes and nutritional support

FEBRILE NEUTROPENIA

Definition

- a single oral temperature measurement of **≥38.3° C** (101° F) or
- a temperature of **≥38.0° C** (100.4° F) sustained over 1 hour or
- a temperature of ≥38.0° C (100.4° F) occur twice within 24 hour

Plus

- An ANC **< 500/µl** or
- An ANC **< 1000/µl** expected to decrease to < 500/µl over the subsequent 48 hour

Evaluation

- Complete history taking and physical examination
- Investigation
  - Complete blood count with differential.
  - Complete metabolic panel.
  - Hemoculture
  - Clean-catch bacterial urine cultures
  - Other: Gram stain and culture from suspicious skin, oropharyngeal, or CVC sites

    Chest X-ray, Coagulation studies, Lumbar puncture, scope, shunt fluid etc.

Common pathogen in neutropenic patient

Gram positive bacteria	Staphylococci Coagulase-negative spp. Staphylococcus aureus Streptococci Alpha-hemolytic e.g. Streptococcus viridians, Streptococcus mitis
Gram negative bacteria	Enterobacteriaceae, Pseudomonas aeruginosa Stenotrophomonas maltophilia Acinetobacter spp.
Fungus	Candida spp. Aspergillus spp. Zygomycetes Cryptococci Pneumocystis jiroveci

Risk stratification

Patient factors

- Type of malignancy: AML, Pre-B ALL, Burkitt's lymphoma, progressive disease, relapse with BM involvement.
- Type of chemotherapy: HSCT, ALL induction; chemotherapy any chemo more intensive than ALL maintenance therapy.
- Timing of chemotherapy: Given within 7 days prior to onset of febrile neutropenia episode
- Other factors: central venous catheter, age ≤ 5 years

Lehrnbecher T et al. J Clin Oncol 2012

Risk stratification

Episodic specific factors

- Vital signs: Fever > 38.5 ^{o}C; hypotension; tachypnea; hypoxia < 94%
- Other Signs and Symptoms: altered mental status, severe mucositis, vomiting or abdominal pain, focal infection, upper respiratory tract infection
- Laboratory: Hemoglobin: ≤ 7 g/dl; Platelets: < 50,000/μL, WBC: <300 /< 500, ANC < 100/μL
- Imaging: New chest X-ray change

Lehrnbecher T et al. J Clin Oncol 2012

Management in low risk patient

Antibiotic should be start **within 60 minutes**

Oral antibiotics used successfully in children with low risk FN are fluoroquinolones alone; or in combination with amoxicillin-clavulanate

Consider discontinuation of empiric antibiotics in low-risk patients at 72 hours irrespective of marrow recovery status

Lehrnbecher T et al. J Clin Oncol 2012

Management in high risk patient

Antibiotic should be start **within 60 minutes**

- **Monotherapy**
  - **Fourth-generation antipseudomonal β-lactam cephalosporin**
  - **Meropenem**
  - **Piperacillin/tazobactam**
- **Dual therapy** (antipseudomonal β-lactam plus an aminoglycoside)

  - No significant difference in efficacy, toxicity, or mortality found between antipseudomonal penicillins vs cefipime vs carbapenems
  - Ceftazidime monotherapy should not be used if there are concerns of Gram-positive or resistant Gram-negative infections.

Lehrnbecher T et al. J Clin Oncol 2012

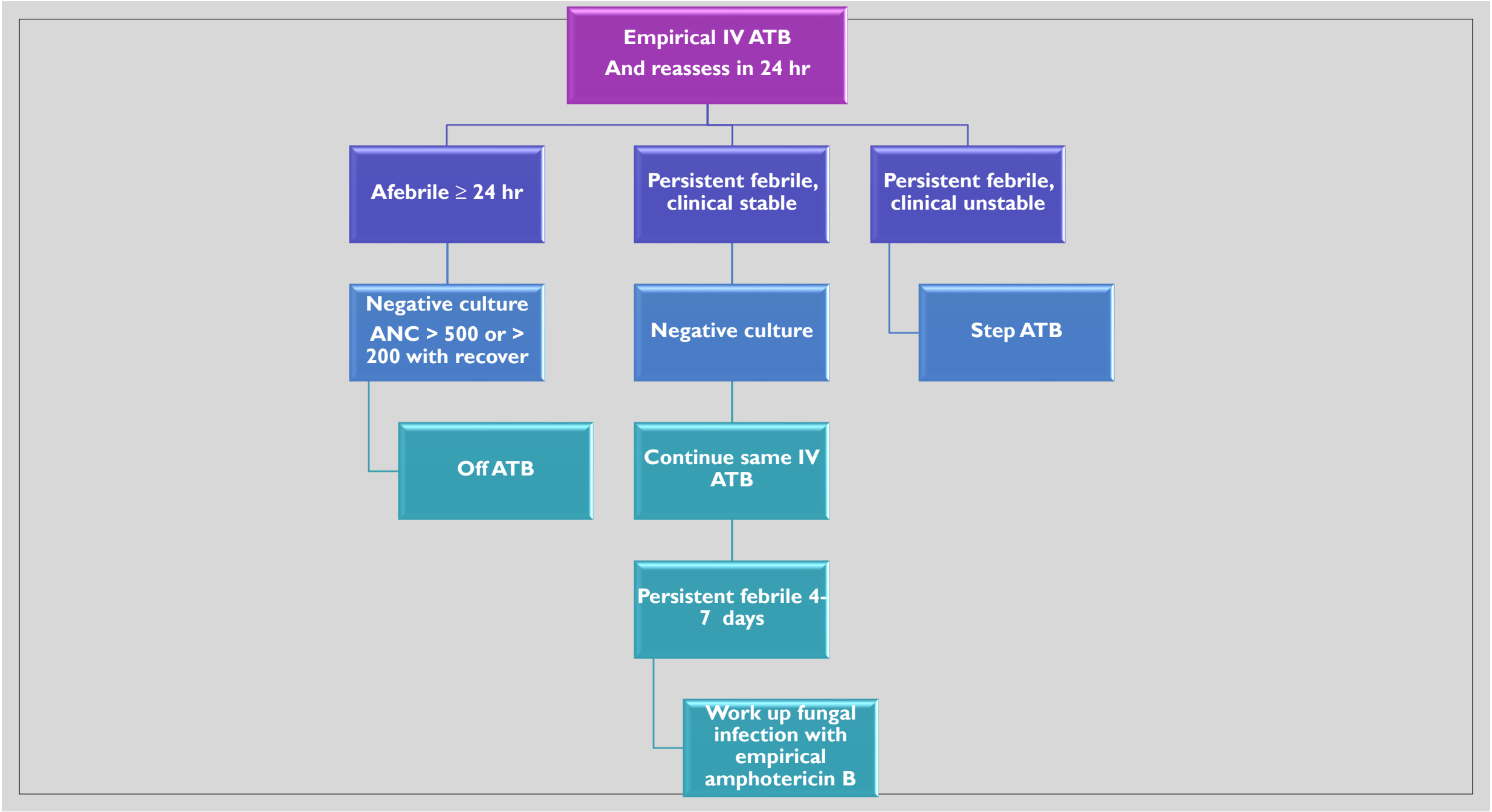
Antibiotic

Vancomycin

- **AML**
- **Shock**
- **Mucositis.**
- Prior history of **alpha-hemolytic Streptococcus** infection.
- **Skin breakdown** or catheter site infection.
- Colonization with resistant organisms treated only with vancomycin.
- **Vegetations** on echocardiogram.
- **Severe pneumonia**.

Anaerobic drug

- Typhlitis
- Significant mucosal breakdown.
- Perianal skin breakdown.
- Peritoneal signs or other abdominal pathology
- C. difficile infection.


Empirical IV ATB
And reassess in 24 hr
Afebrile ≥ 24 hr
Persistent febrile, clinical stable
Persistent febrile, clinical unstable
Negative culture
ANC > 500 or > 200 with recover
Negative culture
Step ATB
Off ATB
Continue same IV ATB
Persistent febrile 4-7 days
Work up fungal infection with empirical amphotericin B

Management

- Afebrile ≥ 24 hr
- Negative culture at 48 hr
  ANC > 500 or > 200 with recover
- Off Antibiotic

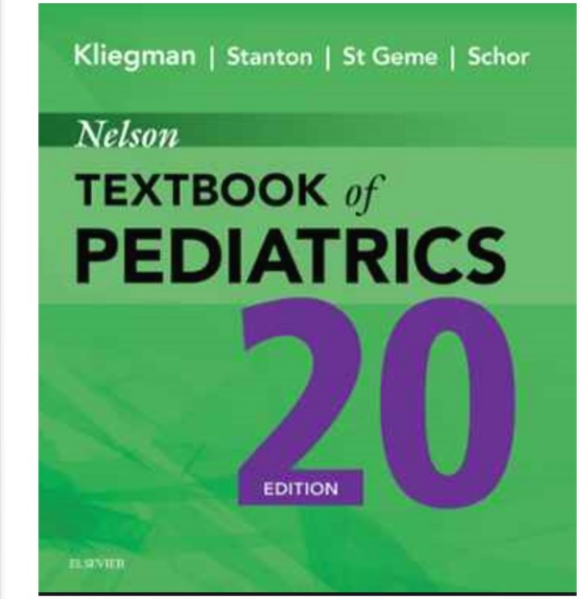
Management

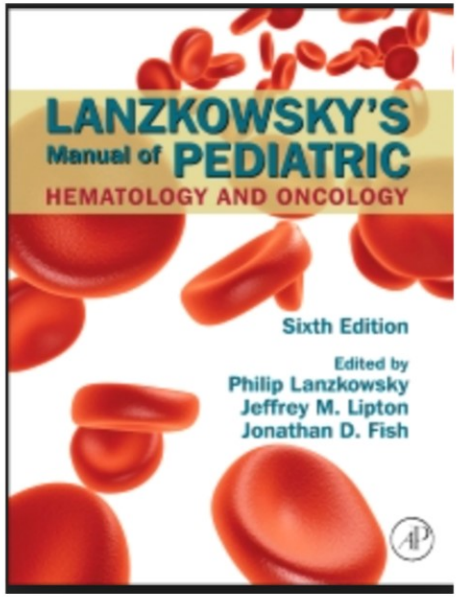
- Persistent febrile, clinical stable
- Negative blood culture at 48 hr
- Continue same IV antibiotic
- Persistent febrile ≥4 days
- Work up fungal infection with empirical amphotericin B

Management

- Persistent febrile, clinical unstable stable
- Step antibiotic
- Persistent febrile ≥4 days
- Work up fungal infection with empirical amphotericin B

Reference





เอกสารประกอบการสอน เรื่องภาวะฉุกเฉินในผู้ป่วยมะเร็งเด็ก ของ อ.พญ.ปิยธิดา วงศ์มาศ

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Thank you for your attention