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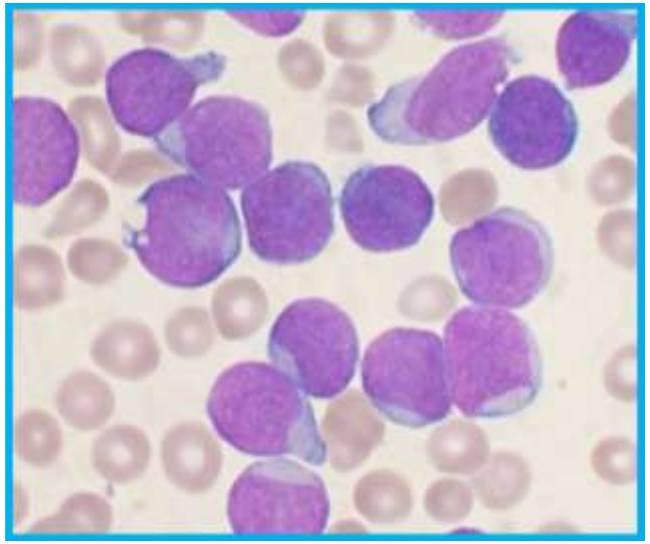
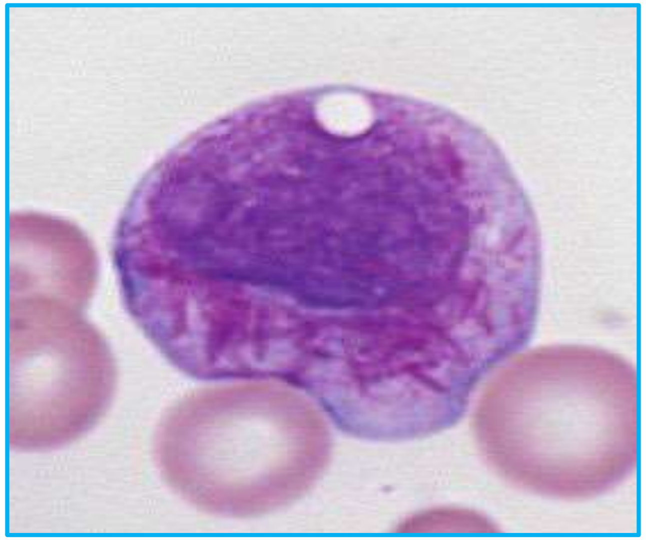
Haematology emergencies





UNIVERSITY of NICOSIA | MEDICAL SCHOOL

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MED-601

DECEMBER 2019

Learning Objectives

Emergencies in Haematology:

- Sickle cell crisis
- Neutropenic sepsis
- Acute Promyelocytic Leukemia and ATRA syndrome
- Tumor Lysis syndrome

Case Nr .1

- A 25-year-old man with a history of Sickle cell anaemia presents to A&E with **generalized acute pain** which is ranked 9 out of 10 on the pain scale.
- The patient complains of malaise over the last 3 days and the pain did not improve with medication that he had at home (oramorph and ibuprofen).

What next ?

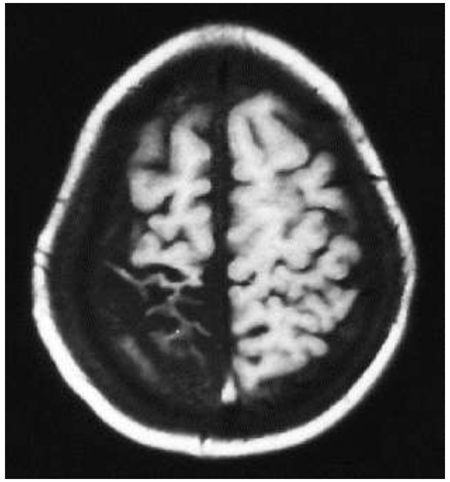
- What's wrong with him?
- What are you worried about?
- How serious an illness is SCD?
- What do you know about how SCD presents and affects patients?

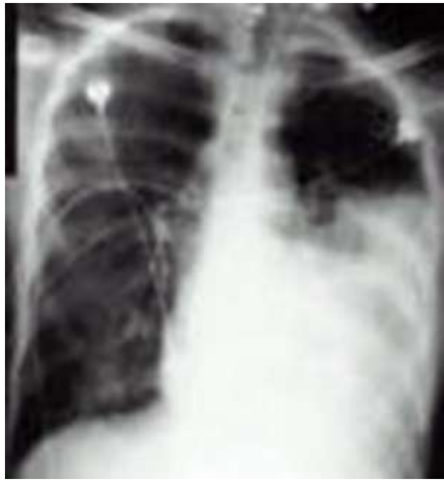
Sickle cell disease is a multi system disorder

- Sickle cell anaemia is a **haemolytic anaemia** with
  - ↑**reticulocytes** and ↑ bilirubin that causes jaundice

- Reticulocytes express higher level of adhesion molecules than mature RBC
  → **vascular occlusions**

- Microvascular occlusions lead to:
  - **hypoxia**→ **Fatty changes** in heart, liver, kidney
  - **ischemia and infarction** →**acute pain episodes**
  - **multiple infarcts in different organs:**
    - **in spleen** which cause fibrosis and **autosplenectomy**
    - **In chest** leads to **acute chest syndrome**
    - **In kidney** leads to **kidney failure**





Sickle Cell Disease - Types of cell crises

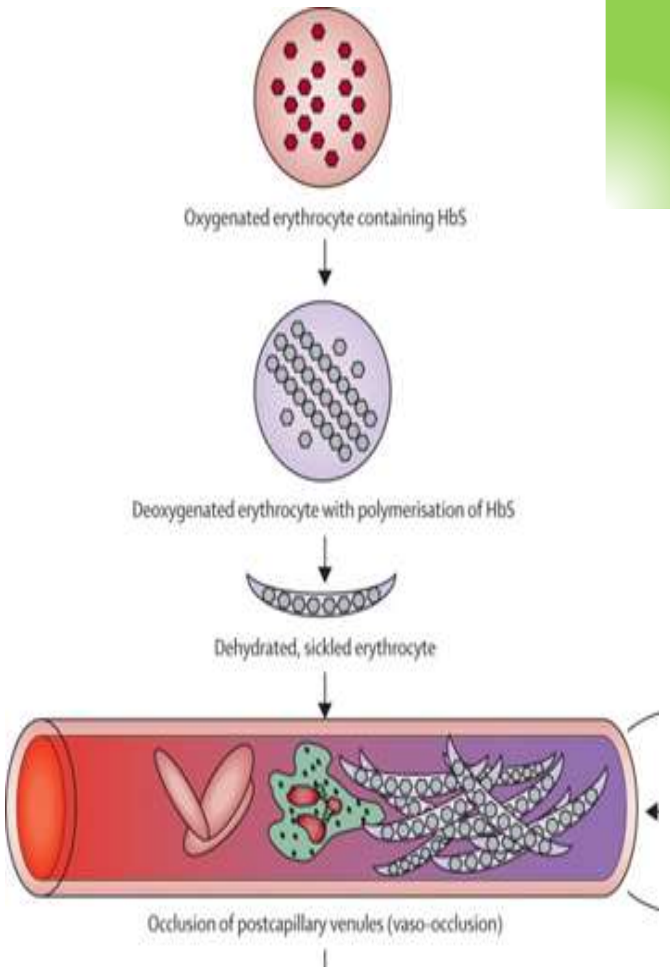
- 1. Vaso-occlusive, thrombotic painful crises
- 2. Sequestration crises
- 3. Aplastic crises
- 4. Haemolytic crises

1.Vaso-occlusive, thrombotic or painful crises

- the **most frequent**
- episodes of **hypoxia** and **infarct**

➔ **severe pain** in affected area

- **precipitated by:**
  - **Infection**
  - **Dehydration**
  - **Acidosis**
  - **Deoxygenation:**
    - altitude, operation, stasis, exposure to cold

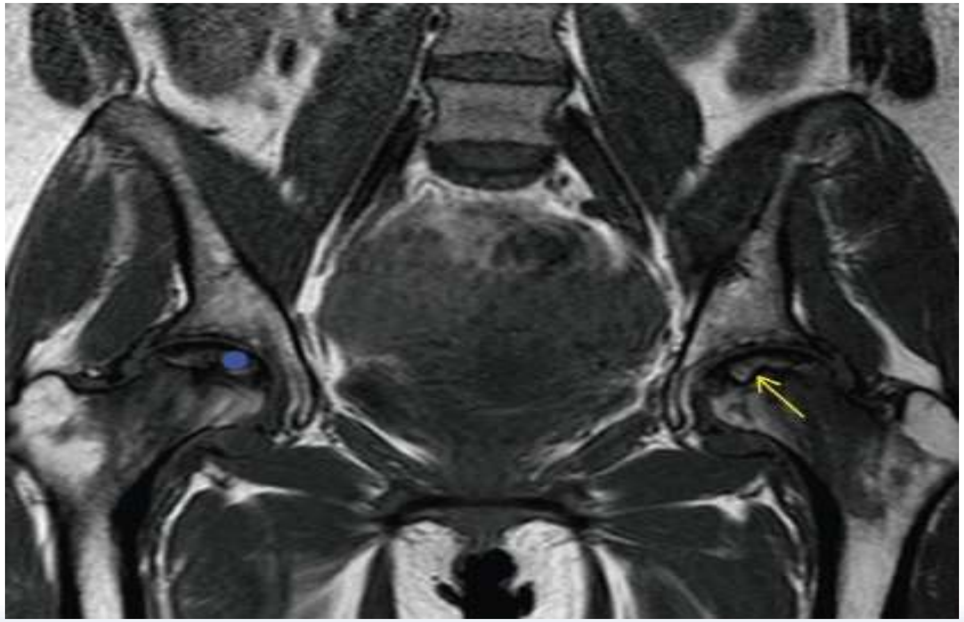


Bone pain

- is the most common and is due to bone marrow infarction

"Hand-foot syndrome"
painful dactylitis

"Avascular necrosis"
of femoral & humeral head



What next ?

- What Questions should be answered?
- What investigations?
- What treatment?
- What order and when to do?

Assessment and pain management

- **Pain scores** ➔ Early, adequate,
  - patient analgesia - personalised
  - What have they already tried,
  - what do they know works
- **Think of triggers**
- **Other causes of pain** – non SCD related
- **Re-review** – 2nd dose of pain relief
- **Management of opioids** on the ward
  - Toxicities

Care pathway for urgent pain relief for patients with Sickle Cell disease

- This pathway has to **be individualized**
- Our **target time**
- from the **presentation**-

to **analgesia provision**

is 30 minutes

Sickle cell pain episode - Management

- **Assess pain** and **treat rapidly within 30** minutes **of arrival**
- Opioid analgesia
- Starting dose based on patient's prior pain and dosing requirements
- Frequent reassessment and dose escalation (within 20 min)
- Patient control analgesia is optimal
- **Assess volume status**; hydration with normal saline if needed

- **Assess for** and **initiate treatment** of potential **precipitating conditions:**
  - Infection
  - Acute chest syndrome
  - Stroke
  - Bone marrow suppression with reduce reticulocyte count
  - Hepatic or splenic sequestration
  - Cardiomyopathy
  - Organ injury or hemodynamic instability

- **Precipitating conditions** requires **inpatient management? OR**
- **Inadequate pain control** with escalating therapy **for two hours**

YES→ ADMIT

NO→ OUTPATIENT management

Inpatient Management plan

- ▶ **"Around the-clock"** continuous or regularly scheduled **intravenous infusion of morphine**
  - **Morphine 0.1 to 0.15mg/kg IV** (maximum single dose of 10mg)
- ▶ **Fentanyl 1.5mcg/kg intranasal** (up to two doses 5-10min apart, maximum single dose 100mcg)
  - Is rapid-acting, has a short duration of action
  - Avoids delays associated with obtaining iv access mostly in children > 3 years
- ▶ **Fentanyl intravenously** is the opioid of choice in renal or hepatic insufficiency
- ▶ **Additional PCA Patient Control Analgesia** demand dose equivalent to one-sixth of the hourly dose
- ▶ **20 min lockout** period for demand **dosing**

- ▶ **Therapy for precipitating** conditions
- ▶ Monitor for **sedation**
- ▶ Provide **incentive spirometry**
- ▶ Provide stimulant **laxatives**
- ▶ Venous thromboembolism **VTE prophylaxis** if appropriate
- ▶ **Convert to oral dosing** when iv doses approaches equal analgesic home regimen

Up to date

Case Nr.1 after a couple of days

- Patient is admitted to ward
- Receiving regular pain relief
  - morphine injections every 2-3 hours
- Pain in arms and legs improving
  - dose reducing
- **Next morning** – nurses on ward ask you to see the patient:
  - **Temp 39.0ºC**
  - **RR 32 rpm**
  - **HR 120 bpm**
  - **$SpaO_2$ 82%** on room air, 96% on 6L/min O_2
  - Patient complaining **of central sternal chest pain**

What next?

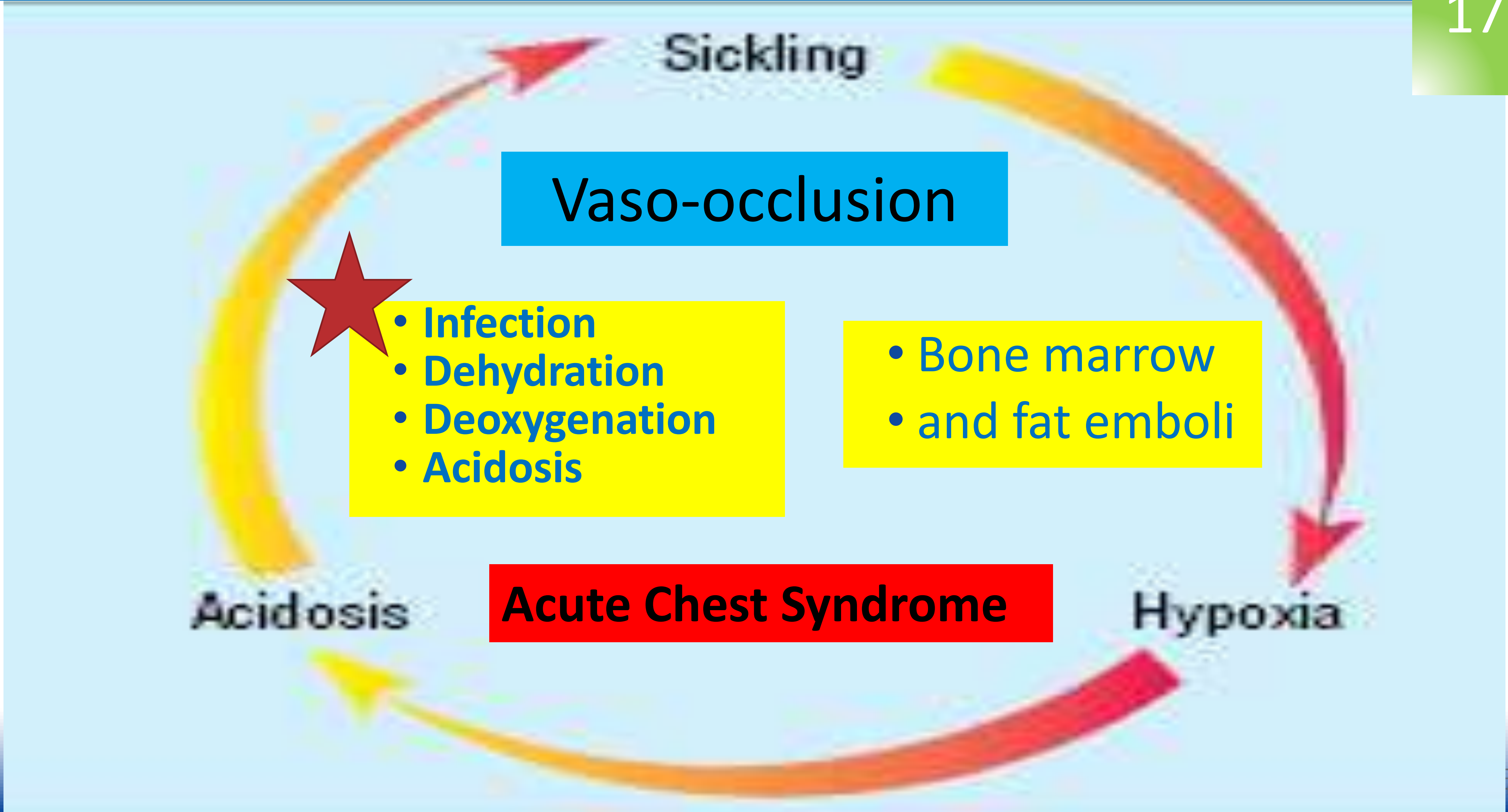
- What's the most probable cause of patient's symptoms?

Acute chest syndrome ACS

► ACS can be defined as:

- **a new infiltrate** on chest x-ray due to **infarct** (vaso-oclusion)
- associated with **one or more new symptoms**:
  - ✓ fever,
  - ✓ chest pain
  - ✓ cough,
  - ✓ sputum production,
  - ✓ dyspnea,
  - ✓ Hypoxia (oxygen saturation <95%)

Pathophysiology of ACS



Vaso-occlusion

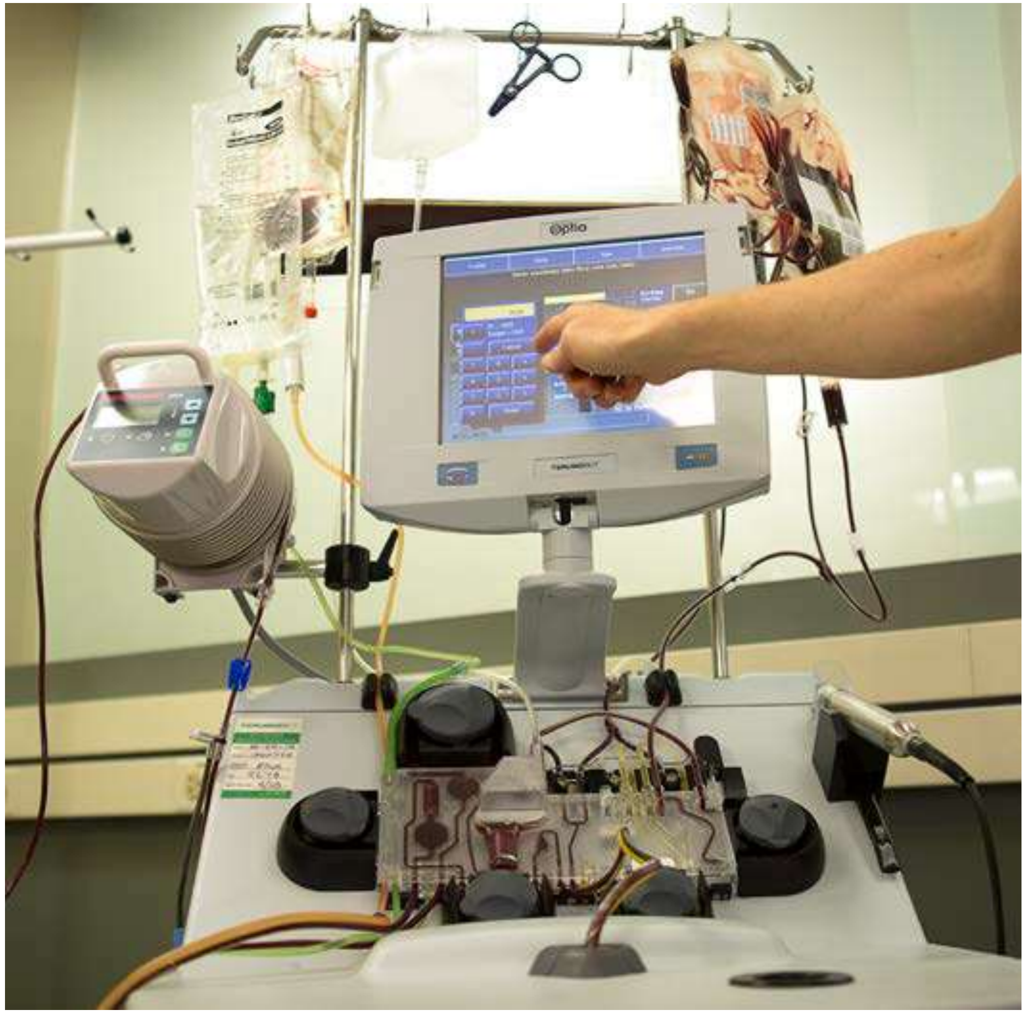
- **Infection**
- **Dehydration**
- **Deoxygenation**
- **Acidosis**

- Bone marrow
- and fat emboli

Acute Chest Syndrome

Acute chest Syndrome – a medical emergency

- **Pain relief,**
- **Consider antibiotics**
  - co-amoxiclav + clarithromycin or
  - Levofloxacin alone if penicillin allergy
- Fluid therapy
- **Physiotherapy**
- **Non-invasive ventilation**
- **Blood transfusion**
  - Increase Hb & oxygen carrying capacity
  - Reduce percentage of HBS

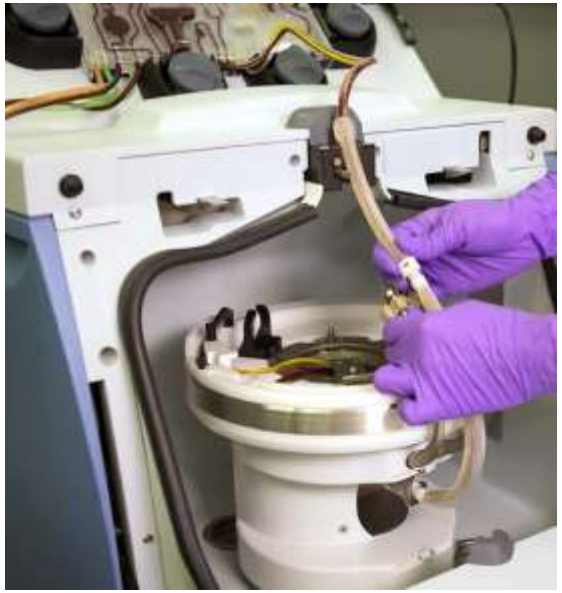


http://hospital.blood.co.uk/media/29205/auto-rbcx-sickle-cell-flyer.pdf

- **Automated Exchange transfusions**

Benefits of automated RBC exchange :

- Accurately **predicts** a patient's final **Haematocrit** and **final HbS**
- Continuously **manages** and **maintains a patients fluid** balance
- **Short procedure time** (average 98mins)
- **Small extracorporeal volume**
- **Less iron overload**
- **Prevents/improves symptoms of crises**
- **Treats and prevents complications** of Sickle Cell Disease.



Case Nr. 2

- A 4-year-old boy with a history of Sickle cell anaemia presents to the A & E with **acute pain on Left upper quadrant (LUQ)** area. The pain is also associated with left shoulder pain.
- The parents of the child complain that he has **high fever** and has **vomited** twice since morning.
- On examination there is tenderness in the left upper quadrant with a **mass palpable 4cm** under the left hypochondrium.

	Previous admission	**Current Admission**
Hb (g/dL)	9.0	6.5
Reticulocytes (%)	1.5%	5%
Palpable mass LUQ	1cm	4cm

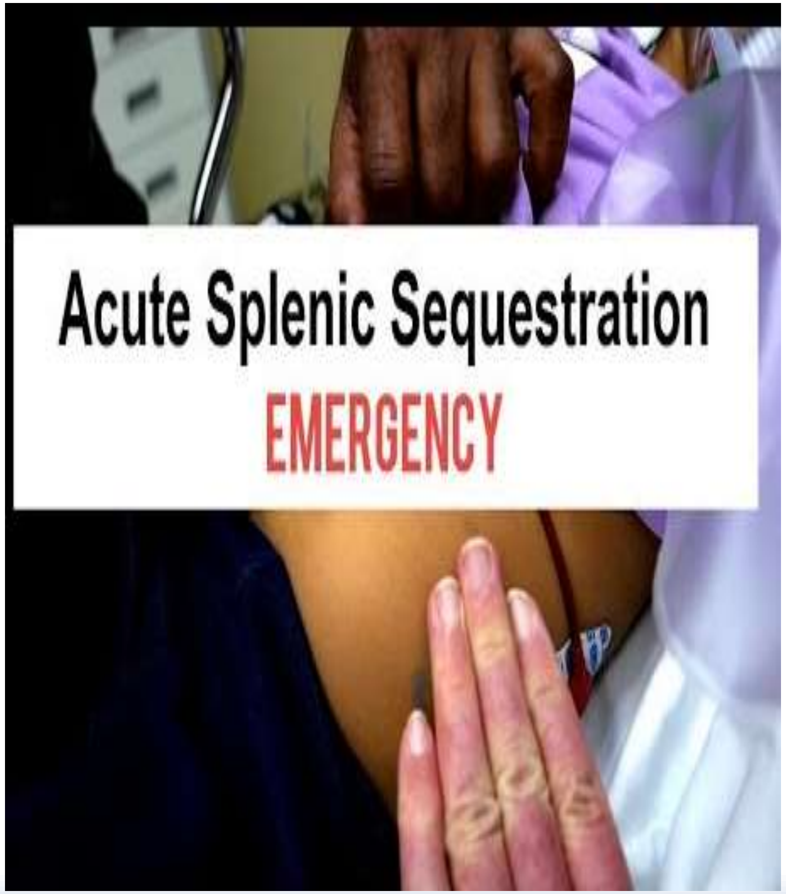
Based on the blood results given what is the more likely diagnosis?

A. Aplastic Crisis.
B. Haemolytic crises.
Splenic Sequestration Crisis.
D. Strep. Pneumoniae infection.
E. Vaso occlusive crisis.

2. Sequestration crisis

Acute Splenic sequestration is defined as:

- **a rapid enlargement** of the spleen **grater than 2cm** from the steady-stage level
- with **fall in haemoglobin** level at least **with 2g/dL or 20%** from baseline level
- accompanied with **reticulocytosis**
- **Regression of splenomegaly** after **blood transfusions**



Sequestration crisis

- Sickled red blood cells are trapped in the spleen → **Congestion** → thrombosis → infarction → mark hypoxia → continue scarring → **shrinkage of the spleen** → **“autosplenectomy”** by adolescent.
- occurs in infants and young children from **5 months to 5 years**
- leads to **intense haemolysis, hypovolemic shock and death** within hours of the onset
- **Prompt treatment** with **volume expanders** and **blood transfusion** reverse the hypovolemic shock and lead to **regression** of the splenomegaly over a fairly **short period of time**.
- **Splenectomy** should be considered if the child has had more than one episode.

Case Nr. 3

- ▶ A 4-year-old girl is brought to the emergency department because of fever and severe pain in her fingers and toes.
- ▶ Treatment with morphine is started and the girl's symptoms are partially relieved.
- ▶ Physical examination shows a raised facial rash.
- ▶ Laboratory examinations shows:
  - **Hb: 4.0g/dL** and
  - **Reticulocytes: 0,5%**.
  - **Bone-marrow aspirate:** shows **no erythroid precursor cells.**

Infection with which virus is most likely responsible for these findings?

A. Coxsackie virus.

B. Epstein Barr Virus.

C. Hepadnavirus.

D. Herpesvirus.

. Parvovirus.

3. Aplastic crisis - Definition

- **a sudden fall in haemoglobin** accompanied with **<u>reticulocytopenia</u>**
- mostly due to **Parvovirus B19**
- Other causes may be:
  - **EBV or Streptococcal infection**
  - As well as use of **hydroxyurea**
- infection can be **very serious**
- leads to a **<u>temporary</u> aplastic crisis**
- The virus **replicates in erythroblasts** and <u>temporarily interferes</u> with <u>red blood cell production</u>.
- As the infection resolves the symptoms disappear

Parvovirus B19 the 5th disease

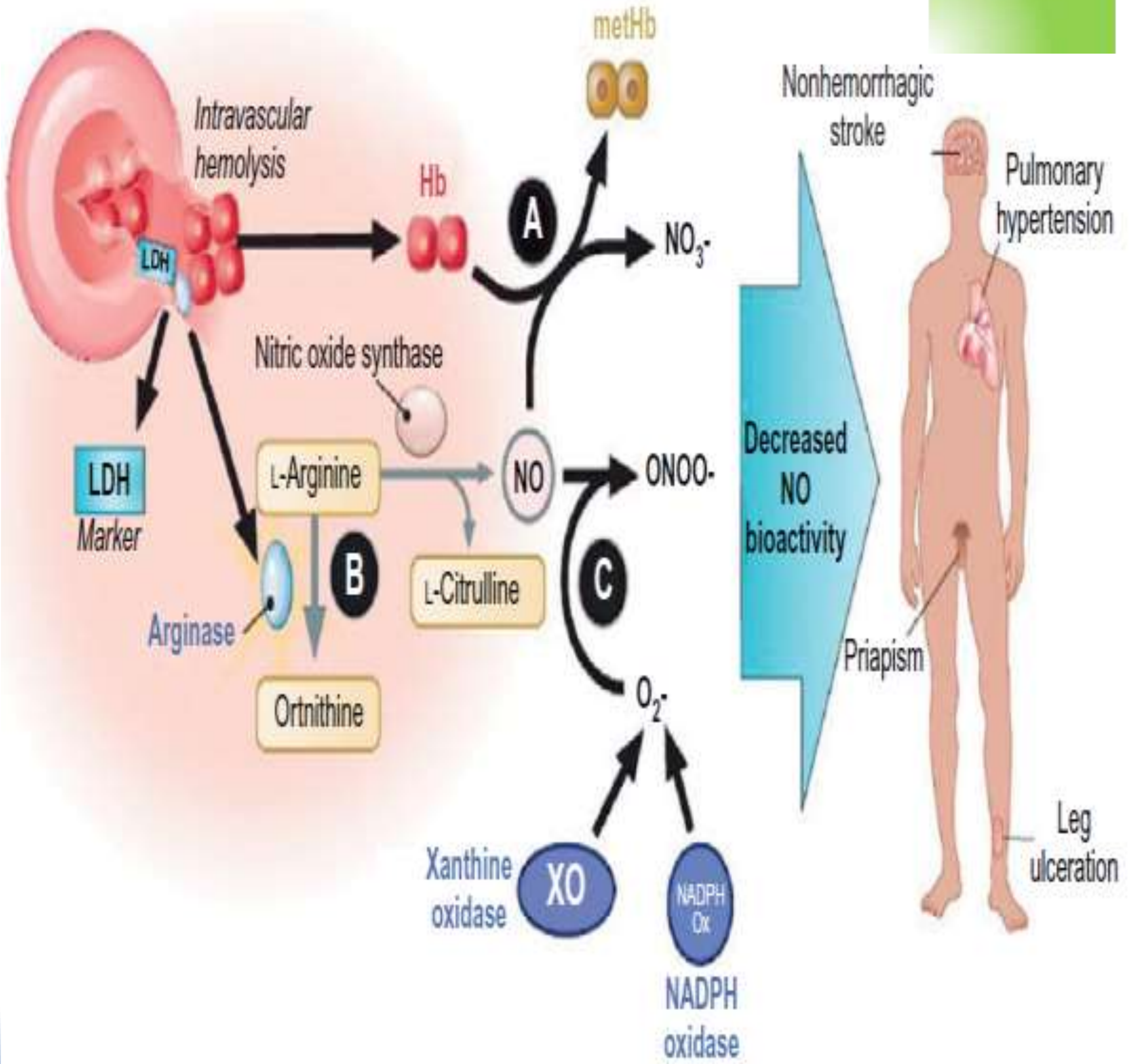
Rash causing children diseases:

1. Measles
2. Scarlet fever
3. Rubella
4. Dukes' disease (≈ like Rubella)
5. Parvovirus

4. Haemolytic crisis - Definition

- a **sudden fall in haemoglobin** accompanied with **reticulocytosis**, hyperbilirubinaemia and **decreased haptoglobin**

- **Free Hb brakes down NO→ increased destruction of NO**
- Arginase released converts Arginine to Ornithine → **decreased production of NO** (Arginine is the substrate for NO)
- **NO is responsible for :**
  - **vasodilation in blood vessels and**
  - **smooth muscle relaxation**
- **NO depletion :**
  - **vasoconstriction** and **muscle spasm**



In general…..Transfusions as URGENT treatment

- Transfusions <u>are not needed </u>for the **usual anaemia** or **mild episodes of pain** associated with Sickle Cell Disease.

- **Transfusion is helpful** in:
  - acute chest syndrome,
  - perioperatively, and
  - during pregnancy.

- **Urgent replacement of blood** is often required for **sudden, severe anaemia** due to:
  - **acute splenic sequestration,**
  - **parvovirus B19 infection, or**
  - **hyperhemolytic crises.**

Case Nr. 4

- A 45 year-old lady is currently being treated for metastatic **breast cancer.**
- Her last chemotherapy was **7 days** ago.
- She presents to A&E with **lethargy** and **myalgia**. She has no cough, dysuria or rashes.
- Her observations today show:
  - Temperature 38.3oC
  - BP: 110/80mmHg
  - Heart rate 110/min

The patient has neutropenic fever and is in risk of developing neutropenic sepsis

What is the appropriate management

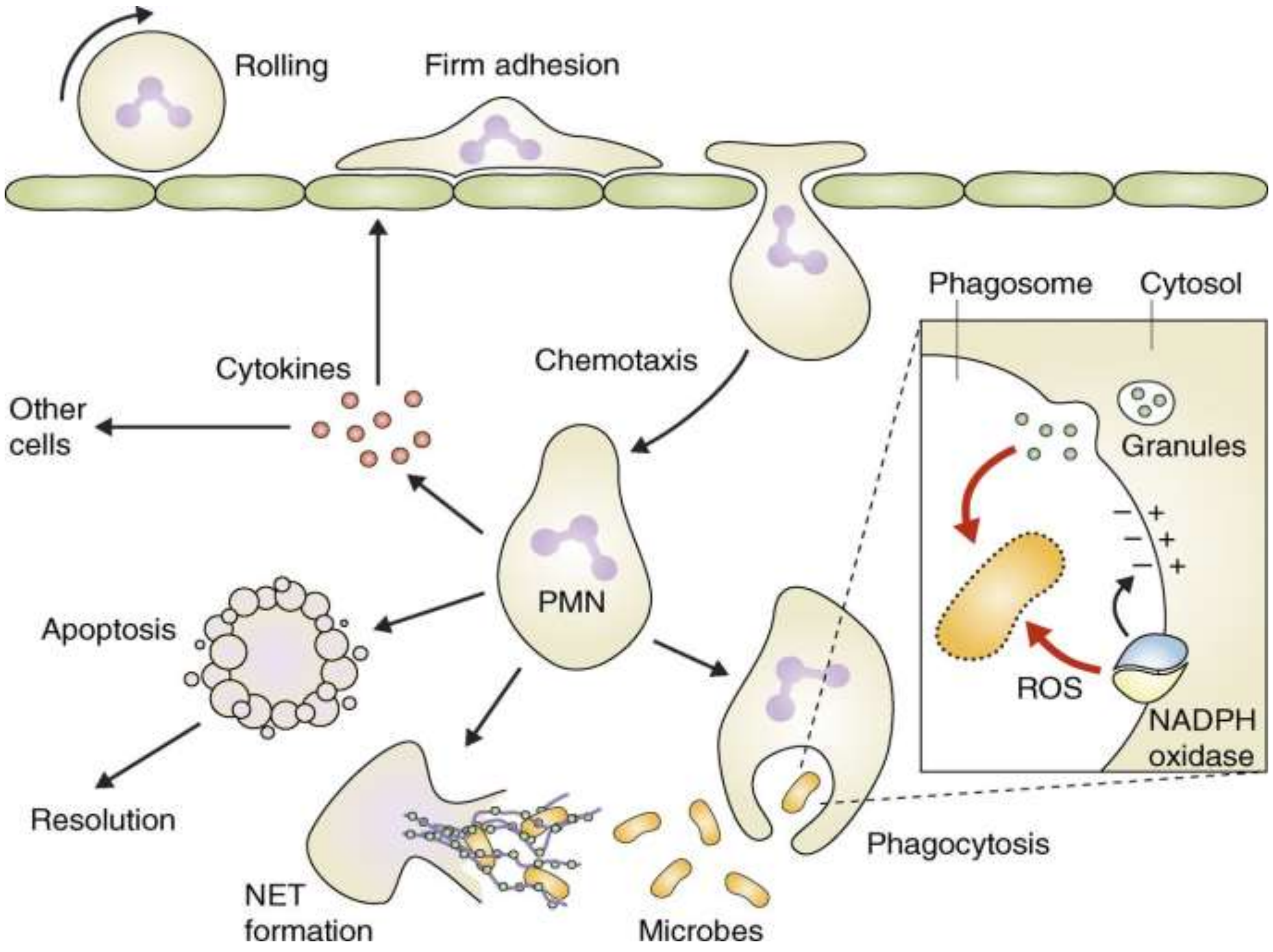
- A. Prescribe co-amoxiclav and review in 1 day
- B. Arrange urgent blood tests , prescribe co-amoxiclav and review in 1 day
- C. Advise to take paracetamol , arrange urgent blood tests and review in 1 day
- D. Send mid-stream urine for culture and prescribe trimethoprim
- Urgent admission to hospital

Neutropenic sepsis NS

- **Sepsis** is a **life-threatening** organ dysfunction caused by a **dysregulated** host response to infection
- **Neutropenia** is defined as neutrophil count **$<1.5 \times 10^9$/l,** but a level of **$<1.0 \times 10^9$/l** is of clinical concern
- **Agranulocytosis** is defined as neutrophil count **$< 0.5 \times 10^9$/l**
- **NS** has a reported **adult mortality** of between **2 & 21%**[1]
- **Mortality** in **patients admitted to ICU** with neutropenic sepsis is **43%**[2]
- Neutrophils are key to the **innate immune system** and are essential to fight bacterial infections

1. NICE guidance Neutropenic sepsis: prevention and management in people with cancer Sept 2012
2. Legrand et al *Critical Care Med* 2012

Neutrophil functions



- ► **Rolling**
- ► **Adhesion**
- ► **Diapedesis:** migration through endothelium
- ► **Chemotaxis:** recruitment to an inflammatory site
- ► Cytokine secretion
- ► **Phagocytosis**

NET: neutrophil extracellular trap
Attila Mócsai J Exp Med 2013;210:1283-1299

In which patients should you suspect neutropenic sepsis NS?

- Patient **unwell** or **pyrexial** T >38°C and
- Likely to be **neutropenic** (neutrophils $<1.0 \times 10^9$/l)
  - Had **chemotherapy** in the last 6 weeks (neutrophil nadir usually **7-10 days** after chemotherapy)
  - **Bone marrow failure** ➔ myelodysplasia
  - **Functional neutropenia**, e.g new diagnosis haematological malignancy
  - On **immunosuppressive agents**

Patient observation & Assessment in Sepsis

SIRS Criteria

Systemic **I**nflammatory **R**esponse **S**yndrome criteria

1) **Temperature**< 36 or >38oC
2) **Heart rate** >90 beats/min
3) **Resp. rate** >20/min
4) **WBC** <4 or >12 X10^9
5) **Confusion**
6) **Blood glucose**>7.7mmol/L in the absence of diabetes

Red flag Sepsis criteria

1) **Systolic BP**<90mmHg
2) **Mean Arterial Pressure**<65mmHg
3) **Heart rate**>130 beats/min
4) **Resp. rate** >25/min
5) **AVPU**: Alert, verbal, pain, Unresponsive
6) **New requirement for Oxygen to maintain O2 saturation >90%**
7) **Lactate** >2

Quick SOFA

Sepsis related Organ Failure Assessment Score

1) Systolic BP< 100mmHg
2) Altered mental state
3) Respiratory rate >22/min

Quick SOFA*:

- simplified version of the SOFA Score ,
- identify patients at high risk for poor outcome

*International Guidelines for Management of Sepsis and Septic Shock:2016

Investigations

Routine

- FBC
- Renal function
- Liver function
- Clotting screen
- CRP
- Lactate

Septic screen

- Bacterial cultures <u>before</u> antibiotics
  - blood cultures, MSU, bacterial swabs
  - blood cultures should be taken peripherally and from indwelling central venous line if present (PICC, Hickman)
- CXR
- Respiratory virus PCR swab
- Atypical serology, urinary Legionella Ag, Pneumococcal Ag

Management of suspected neutropenic sepsis

Time is critical !!

- Neutropenic patients are **at risk** of rapid onset of septic shock, which is potentially fatal
- **Steps to ensure rapid diagnosis and treatment**
  1. **Patient education**
  2. **Medical education** – high index of suspicion, clear pathway for identifying and treating patients rapidly

Information for patients

SOUTH WEST LONDON CANCER NETWORK

This Patient is on CYTOTOXIC CHEMOTHERAPY

Information for patients:

You MUST contact your hospital team URGENTLY if you feel unwell or develop:

- chest pain or difficulty breathing
- temperature greater than $38^{\circ}C$ ($100^{\circ}F$)
- shivering episodes
- flu-like symptoms
- gum / nose bleeds or unusual bruising
- mouth ulcers that stop you eating or drinking
- Persistent vomiting
- four or more bowel movements in 24 hrs
- Come into contact with either shingles or chicken pox

Version April 2010

Neutropenic Sepsis
Integrated Care Pathway (ICP) Targets

- **Arrival to initial observations**
  - 10 minutes
- **Arrival to doctors assessment**
  - 30 minutes
- **From Prescription to administration of antibiotics**
  - 10 minute
- **All patients should receive antibiotics within an hour of arrival**

Antibiotic regimen in Neutropenic sepsis

- **Broad spectrum antibiotics** for gram negative and gram positive and especially pseudomonas
- Additional antibiotics maybe required to cover **atypical lung infections**, perianal infection etc
- 1st line / if penicillin allergy

1st line	if penicillin allergy
Tazocin 4.5g tds IV	Ciprofloxacin 600mg slow IV bds
Amikacin 15mg/kg/day IV	Amikacin 15mg/kg/day IV

- 2nd Line (48hrs later)
  - Meropenem
  - Vancomycin
- 3rd line (96hrs)
  - Consideration of **antifungal therapy**
  - **Change antibiotics?**

Summary for neutropenic sepsis

- Neutropenic sepsis is a **common haematological** emergency
- It is **potentially fatal,** but morbidity and mortality can be avoided by **rapid diagnosis and treatment**
- Mainstay of treatment is **rapid administration of broad** spectrum iv antibiotics and fluid resuscitation
- It is important to **be alert to patients at risk** of neutropenic sepsis

Case Nr. 5

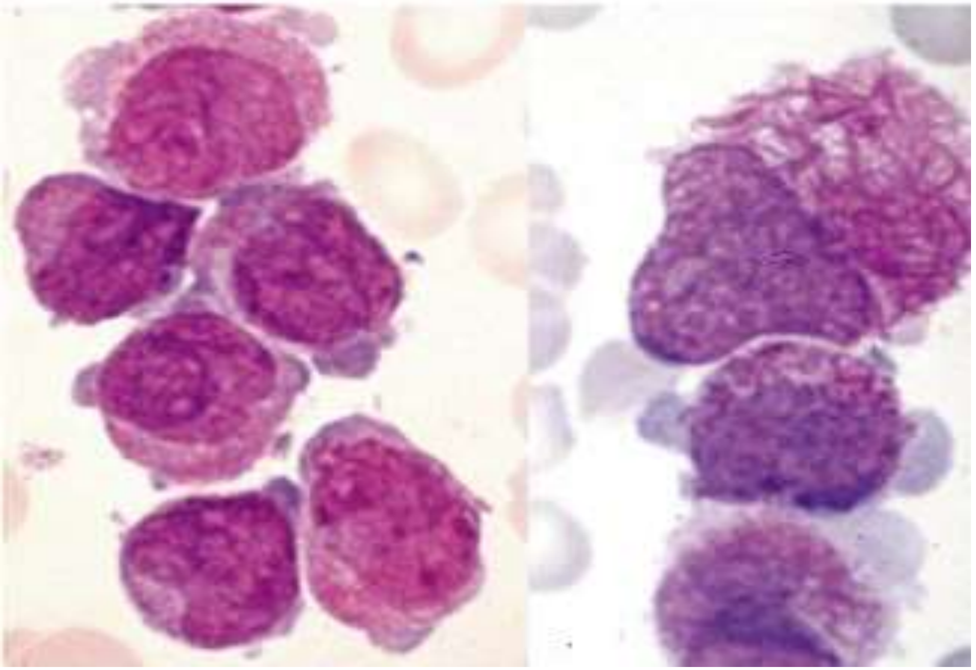
- A 35-year-old man comes to the physician for fatigue and a 1-week history **of gingival bleeding** and **spontaneous bruising**
- He further has decreased appetite and **lost 5 kg** over the past month.
- His **temperature is 38.5° C**.
- Physical exam shows painless axillary and inguinal **lymphadenopathy**.
- His **spleen is palpable** four fingers below the costal margin.

Laboratory studies show:

- Hb 8.3g/l,
- WBC 1.2x10^9/l,
- Neutrophils 0.1x10^9/l,
- Platelets 24x10^9/l
- PT: 22 (11-14s),
- APTT: 55 (28-37s),
- Fibrinogen: 0.1 (1.6-4.8g/l)

Case Nr. 5

► A peripheral smear is shown below:



Which of the following findings is most likely to also be present in this patient?

A. Positive Monospot test

B. Translocation 9;22

C. Peroxidase positive granules

D. Cold agglutinin antibodies

E. Follicular hyperkeratosis

- **Myeloperoxidase**, is found in peroxidase-positive granules, Auer rods → AML
- Increased quantity of Auer rods is found in **AM_3L →in acute promyelocytic leukaemia**
- **Responsible for coagulation complications**.

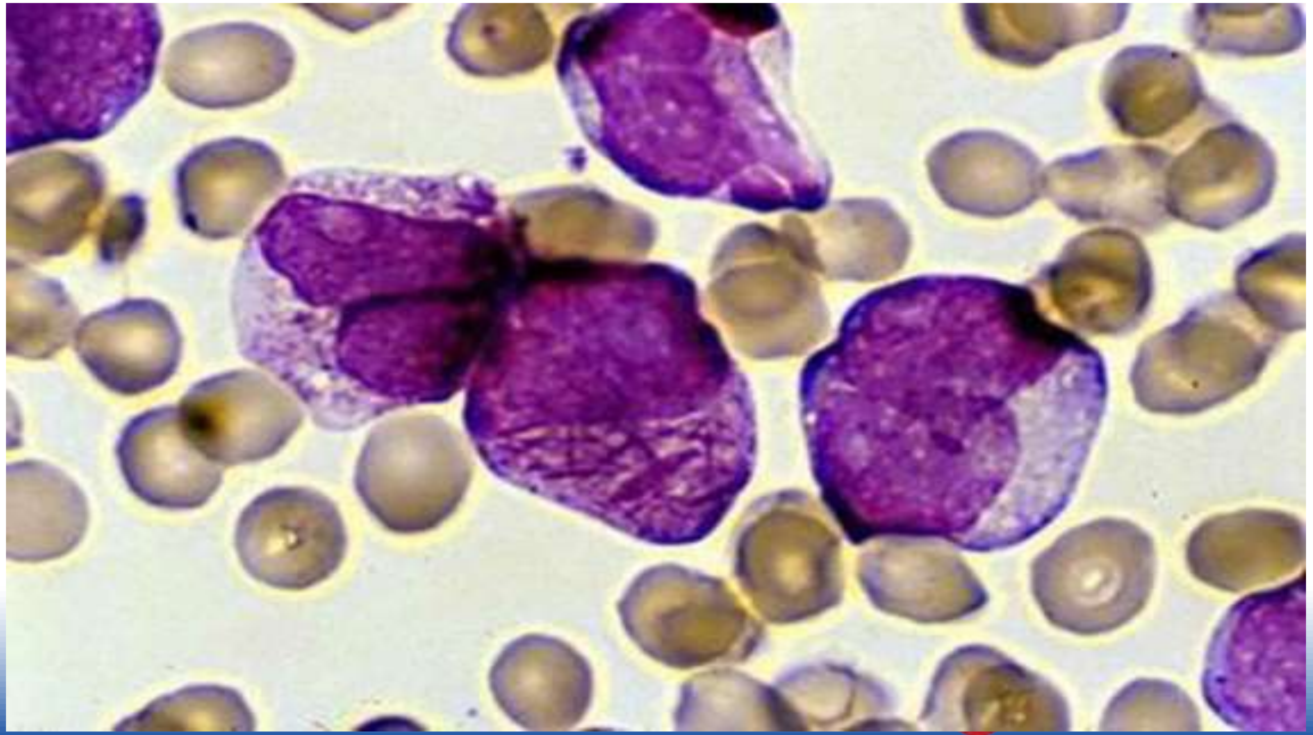
Acute Promyelocytic Leukemia APL

- Typically presents **with leukopenia** bruising and bleeding
- only **10-30%** of patients present with **leukocytosis**
- Characteristic morphology of the promyelocytes with increase number of **Auer Roads**
- Chromosome translocation **t(15;17), PML-RARA fusion**

→ **rearrangement of** retinoic acid receptor

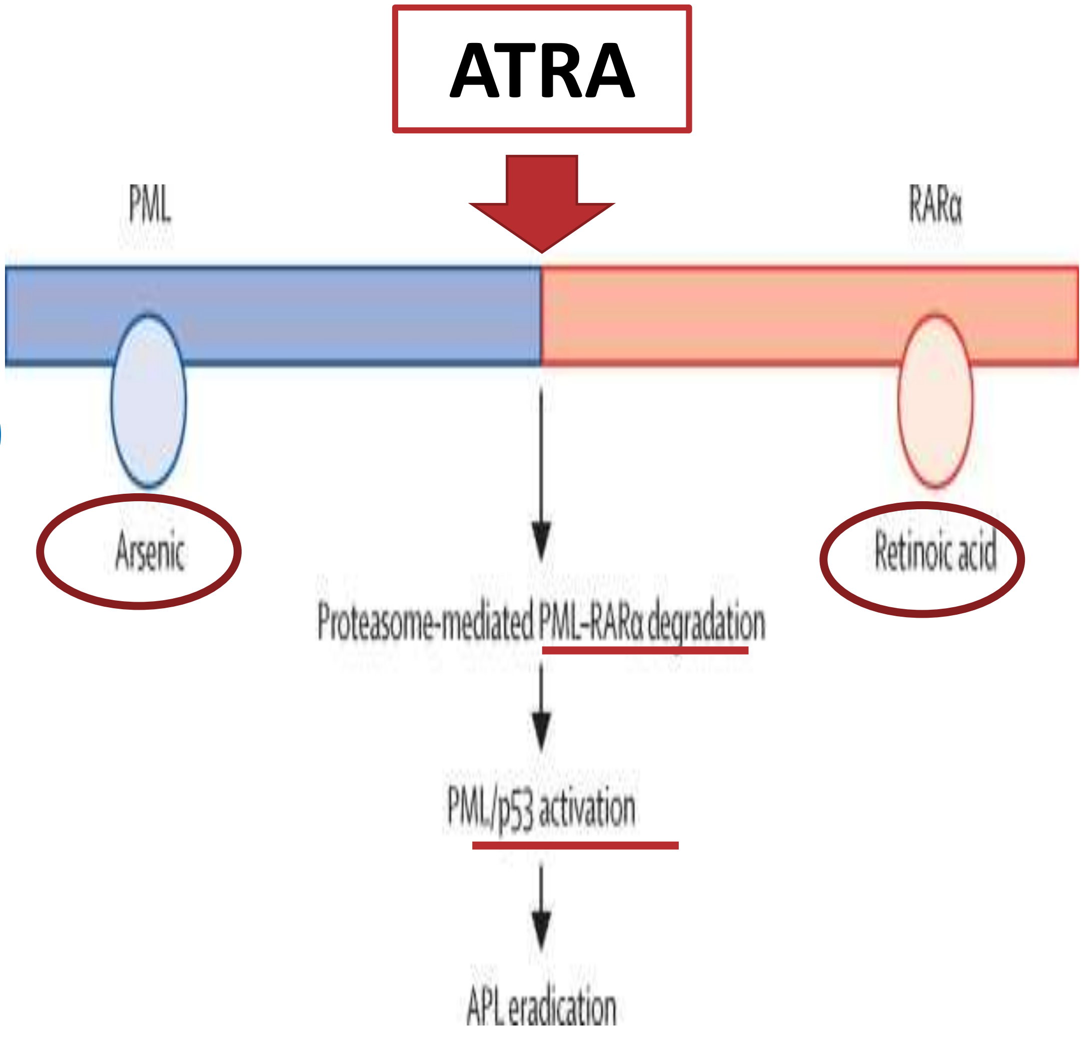
→ **inactivate the p53 → blocks the differentiation at the promyelocyte**

Myeloblast **Pro-Myelocyte** **Myelocyte** **Large promyelocytes with many Auer roads**



APL Acute Promyelocytic Leukaemia M3

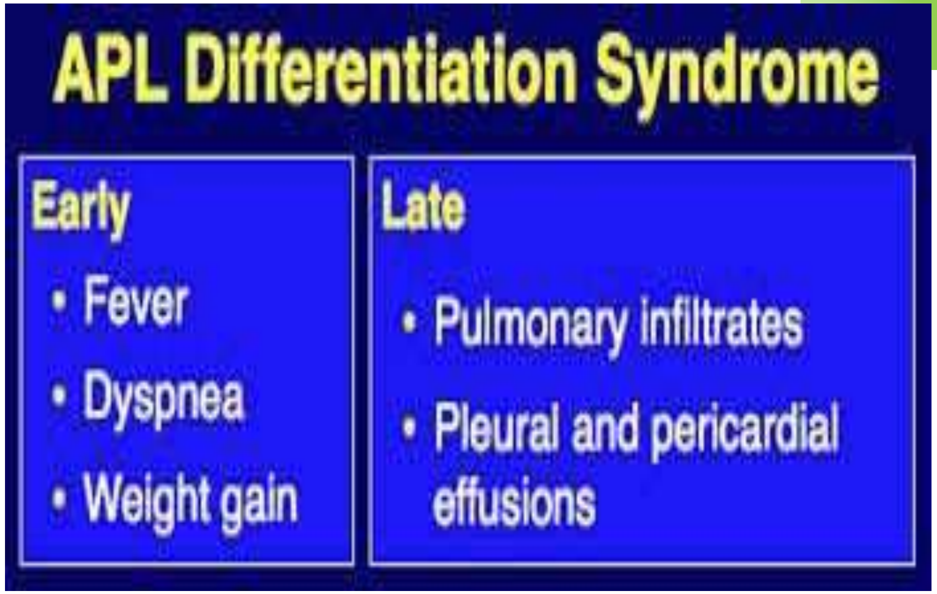
- **Hypergranular promyelocytes** releasing their primary granules full of procoagulant substances lead to **"DIC" disseminate intravascular coagulation .**
- **Treatment** with **All-Trans Retinoic Acid (ATRA) metabolite of Vitamin A** and **Arsenic trioxide** lead to ➔**degradation of the fusion** ➔**liberation of the PML gene**
  ➔that **activate p53** in APL blasts,
  ➔resulting in **leukaemia eradication**
- In adults that achieve a complete remission the **prognosis is better** than the other leukaemias



http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(15)61278-8/fulltext?rss=yes

All Trans Retinoic Acid or ATRA syndrome

- **Acute Promyelocytic leukaemia differentiation syndrome** may arise after **treatment of AML-M3** with **All-trans retinoic acid** due to **Leucocytosis** and **neutrophilia** that results after massive differentiation of promyelocytes



- It is a **systemic capillary leak syndrome** with retention of fluids and peripheral oedema that leads to **pulmonary and renal failure**

- **Treatment:**
  - 10mg Dexamethasone IV twice daily for 3-5 d
  - Discontinuation of ATRA
  - **Concomitant ATRA treatment with chemotherapy** diminishes the risk of ATRA syndrome

ATRA

AML-M3
t (15;17)

Case Nr. 6

- A 35-year-old man is brought to the emergency department with **nausea**, **vomiting, fatigue, and muscle cramps** that began earlier that morning.
- He has a history of hypertension, diet-controlled type 2 diabetes mellitus, and **acute myelogenous leukaemia** for which he has been **undergoing chemotherapy**.
- He smokes 10 cigarettes per day and reports occasionally using marijuana.
- His temperature is 38.7°C, pulse is 85/min, respiratory rate is 25/min, and blood pressure is 110/65 mm Hg.

Laboratory studies show:

FBC:

Leukocyte Count	16,000/mm^3
Hemoglobin	13.4 g/dL
Haematocrit	40.2%
Platelet Count	180,000/mm^3

Serum:

Na^+	135 mEq/L
K^+	5.9 mEq/L
Cl^-	101 mEq/L
HCO_3^-	24 mEq/L
Uric acid	8.5 mg/dL
Creatinine	2.2 mg/dL
Glucose	134 mg/dL
Ca^{2+}	6.8 mg/dL
Mg^{2+}	1.8 g/dL
Phosphorus	8.9 mg/dL

Case Nr. 6

Which of the following would have been most effective in preventing his current symptoms

A. Urine alkalinisation

B. Corticosteroids

C. Rasburicase

D. Allopurinol

E. Intravenous hydration

- **Adequate hydration prior** to receiving chemotherapy helps minimize kidney injury and symptoms preventing **"Tumor Lysis syndrome"**

Tumor Lysis Syndrome

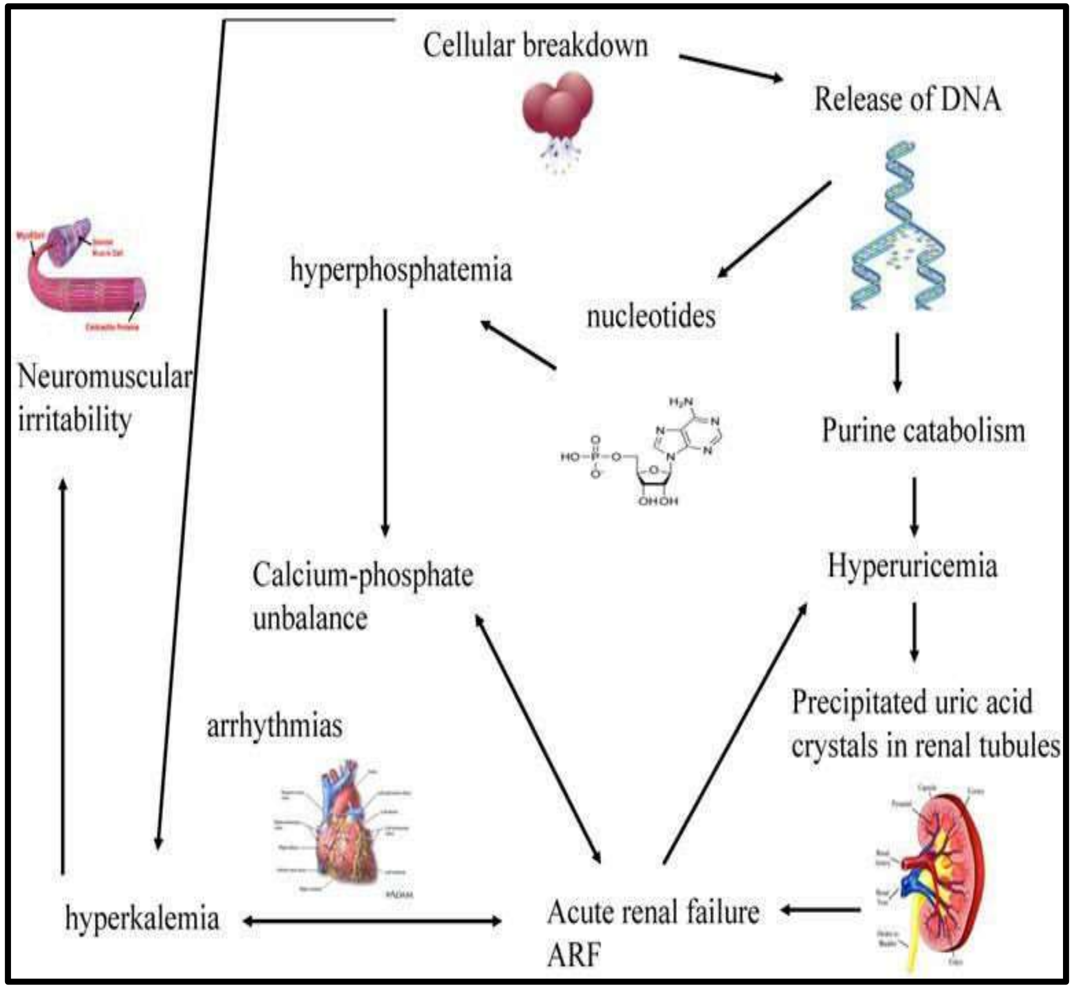
Metabolic emergency resulting from **rapid cell death** and can occur after **chemotherapy**

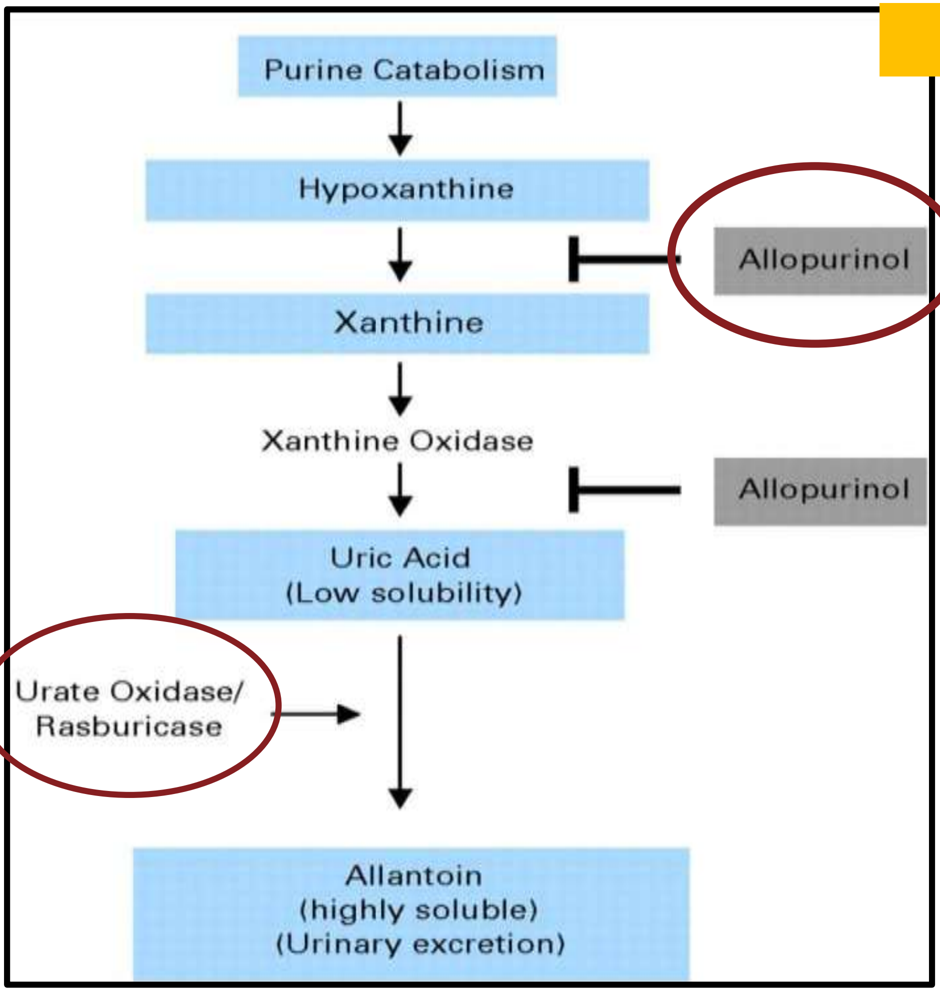
Cairo-Bishop definition of laboratory Tumor Lysis Syndrome for adults

Variable	Value	Change from baseline value	Reference values
Uric acid	≥ 8 mg/dL (476 mmol/L)	25% increase	UA: Up to 7mg/dL
Potassium	≥ 6.0 mEq/L (or 6 mmol/L)	25% increase	K^{+}: up to 5.1mEq/L
Phosphorus	≥ 4.5 mg/dL (1.45 mmol/L) for adults and ≥ 6.5 mg/dL (2.1 mmol/L) for children	25% increase	P^{-3}: up to 4.0 for Adults 6.2 for children up to 10 years
Calcium	≤ 7 mg/dL (1.75 mmol/L)	25% decrease	Ca^{+2}:up to 8.5mg/dL

World J Crit Care Med 2015, May 4; 4(2): 130-138

Tumor Lysis Syndrome - Hyperuricaemia





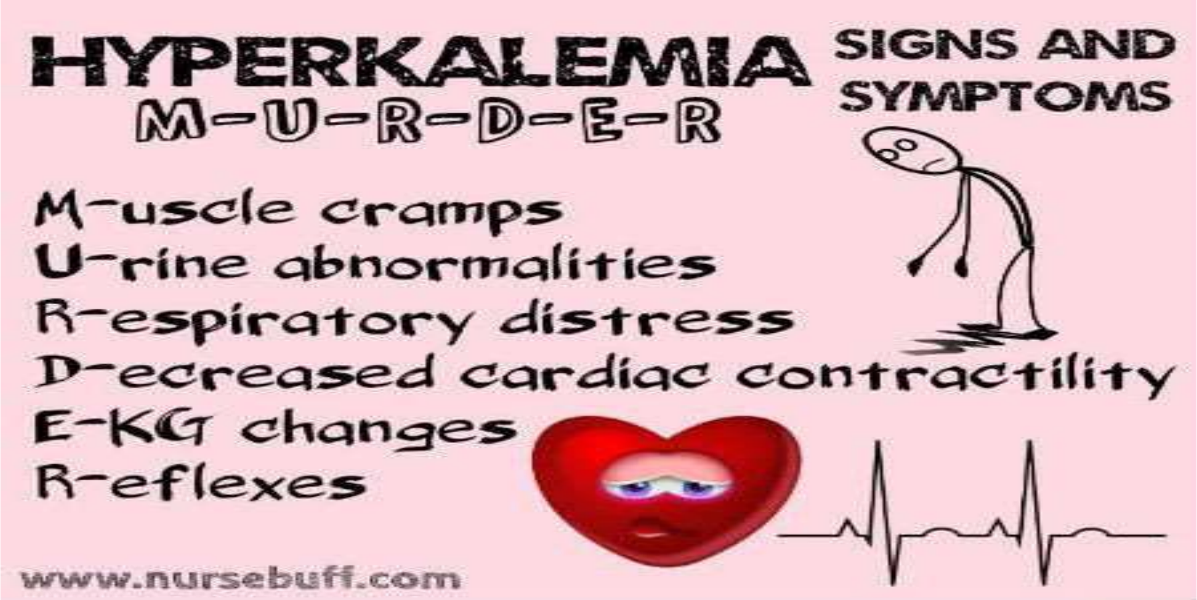
Treatment

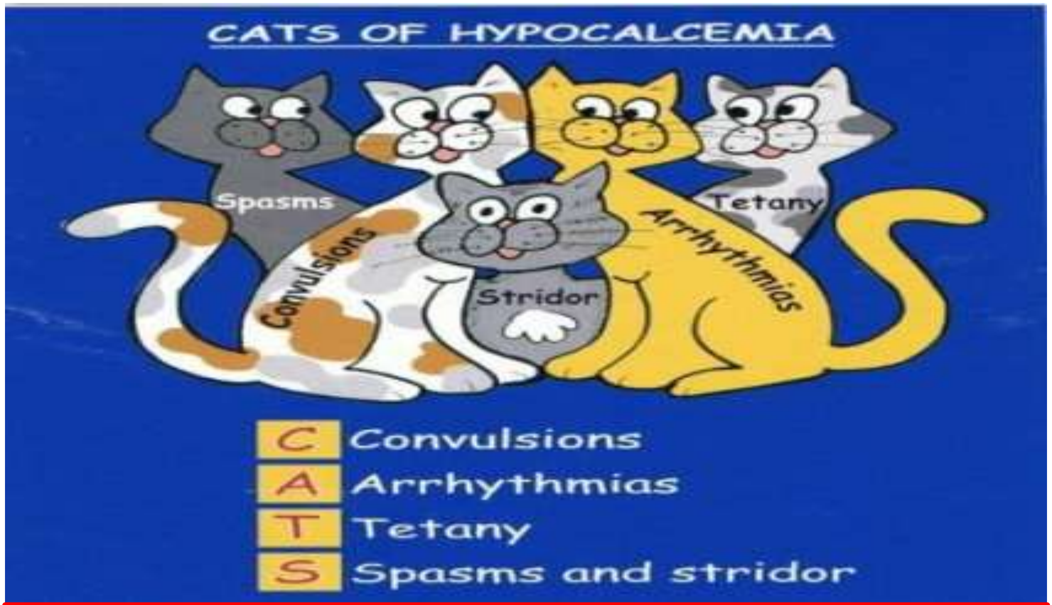
1. Decrease production of uric acid

2. Increased elimination of uric acid

*** Rasburicase is Contraindicated in patients with G6PD deficiency

Tumor Lysis Syndrome – Hyperkalaemia and Hypocalcaemia





**Hyperkalaemia=High Potassium

**Hypocalcaemia=Low Calcium

Treatment:

- adequate **hydration is the most important**
- **uric acid lowering therapies**
- **phosphate binders** and
- minimization of **potassium intake**.
- **dialysis in refractory cases**.

Conclusions

- Most of the haematological emergencies are **rare** but can **present with common symptoms**
- Are **potential fatal** or **life changing** leading to severe sequelae
- **Be aware** and **think about them**
- **Be suspicious** and
- **ACT FAST** to save lives !


Thank You!

Do you have any questions?

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