
بسم الله الرحمن الرحیم

Thalassemia Emergency and Problem oriented approach

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- Guidelines for the Management of Non Transfusion Dependent Thalassaemia (NTDT) Taher A, Vichinsky E, Musallam Ket al., authors; Weatherall D, editor.Nicosia, Cyprus: Thalassaemia International Federation; 2013.

- Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT) .3rd edition,2014. Cappellini MD, Cohen A, Porter J, Taher A, Viprakasit V. TIF Publication NO.20

- Emergency Management of Thalassemia. A,Porter J,Taher A,et al. TIF Publication NO.16

- Medscape 2015

1. Main Leading Pathologies:
    1. Extramedullary Hematopoiesis(EMH)
    2. Thromboembolic events(TE)
    3. Infection
    4. Iron Overload
    5. Acute Transfusion reactions

2. Complaints, Signs &symptoms
    1. Increased transfusion requirements
    2. Fever
    3. Diarrhea, Nausea &Vomiting
    4. Skin rash
    5. Back Pain
    6. Unexplained Abdominal Pain
    7. Chest Pain
    8. Dyspnoea
    9. Worsening jaundice
    10. Leg cramps

Extramedullary haematopoiesis (EMH)

- Compensatory mechanism: bone marrow activity to overcome the chronic anaemia lead to homing and proliferation of Erythroid series in extramedulary tissues and formation of erythropoietic tissue masses
- Mostly in NTDBT (20%); E/B thalass; Non-regular transfused TM;and rarely inHbH disease
- Nearly all of the tissues : spleen, liver , lymph nodes,kidney and peripheral and cranial nerves, brain, and the spinal canal (11 to 15% of cases)
- Emergency problems: neurological problems such as spinal cord compression and paraplegia, and intrathoracic masses
- Paraspinal extramedullary hematopoietic pseudotumors:especial attention due to neural element compression
  - most frequently being reported during the third and fourth decades of life
  - more than 80% of cases may remain asymptomatic
  - male to female ratio reaches 5:1
  - The thoracic region and to a lesser extent the lumbar region are the most commonly involved sites.

EMH: Diagnosis

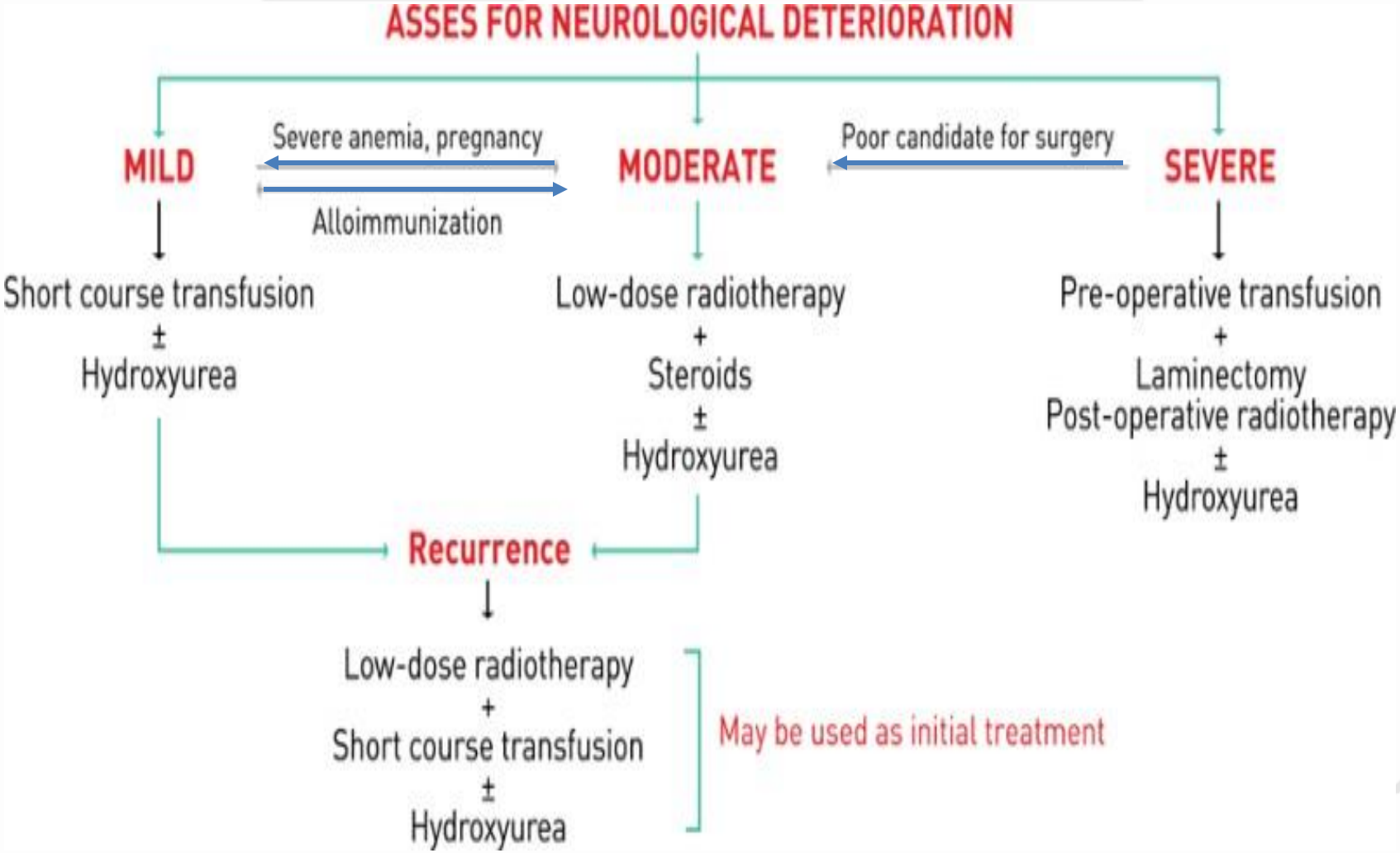
- Magnetic resonance imaging (MRI) is currently the method of choice for the diagnosis and follow-up :
  - Site and extent of the masses
  - Active (have rich vasculature with intermediate signal intensity in both T1- and T2- weighted)
  - Inactive older lesions:(have more fatty tissue with high signal intensity in both T1 and T2 weighted and iron deposits with low signal intensity in both T1 and T2 weighted)
  - Gadolinium is not needed: enhancement is minimal or absent differentiating it from other epidural lesions such as abscesses or metastases

- Biopsy remains the gold standard for establishing a tissue diagnosis:
  - invasive procedure :risk of catastrophic hemorrhage
  - Only reserved for:
    - Older patients with a high probability of malignant disease
    - Cases in which the clinical and radiological picture is equivocal
    - solitary, unilateral active lesion

EMH: management

- **Transfusion therapy : Target Hb >10 g/dl**
  - **Principal treatment modality**
  - **Both treatment and diagnosis**
  - **unable to reverse preexisting cord compression**
  - **Slow :Its role in acute onset symptoms are limited : only as an adjunct to surgery (preparation and/or postoperative course)**
- **Hydroxyurea: patients who are unable to receive blood transfusions due to alloimmunization**
- **Low dose Radiotherapy (900 to 3500 cGy):**
  - **Low dose recurrence up to 19-37%**
  - **risks of radiotoxicity on an already compressed and injured spinal cord :**
    - **Tissue edema :minimized by concomitant high-dose steroid therapy**
    - **myelosuppresion**
  - **Rapid therapeutic response neurological improvement in 50% of cases during 3 to 7 days**
  - **post-operative adjunct following laminectomy to reduce the likelihood of recurrence**
- **combination therapy of any two of the three modalities either in reccurence or as the initial treatment**
- **Surgical intervention:**
  - **Acute presentation which do not respond to adequate transfusion or radiotherapy**
  - **Risks: bleeding within a high vascularity of the mass; incomplete excision due to diffuse involvement;risk of extensive laminectomy,etc.**
- **JAK2 inhibitors**

Algorithm for the management of paraspinal extramedullary hematopoietic pseudotumors in patients with NTDT

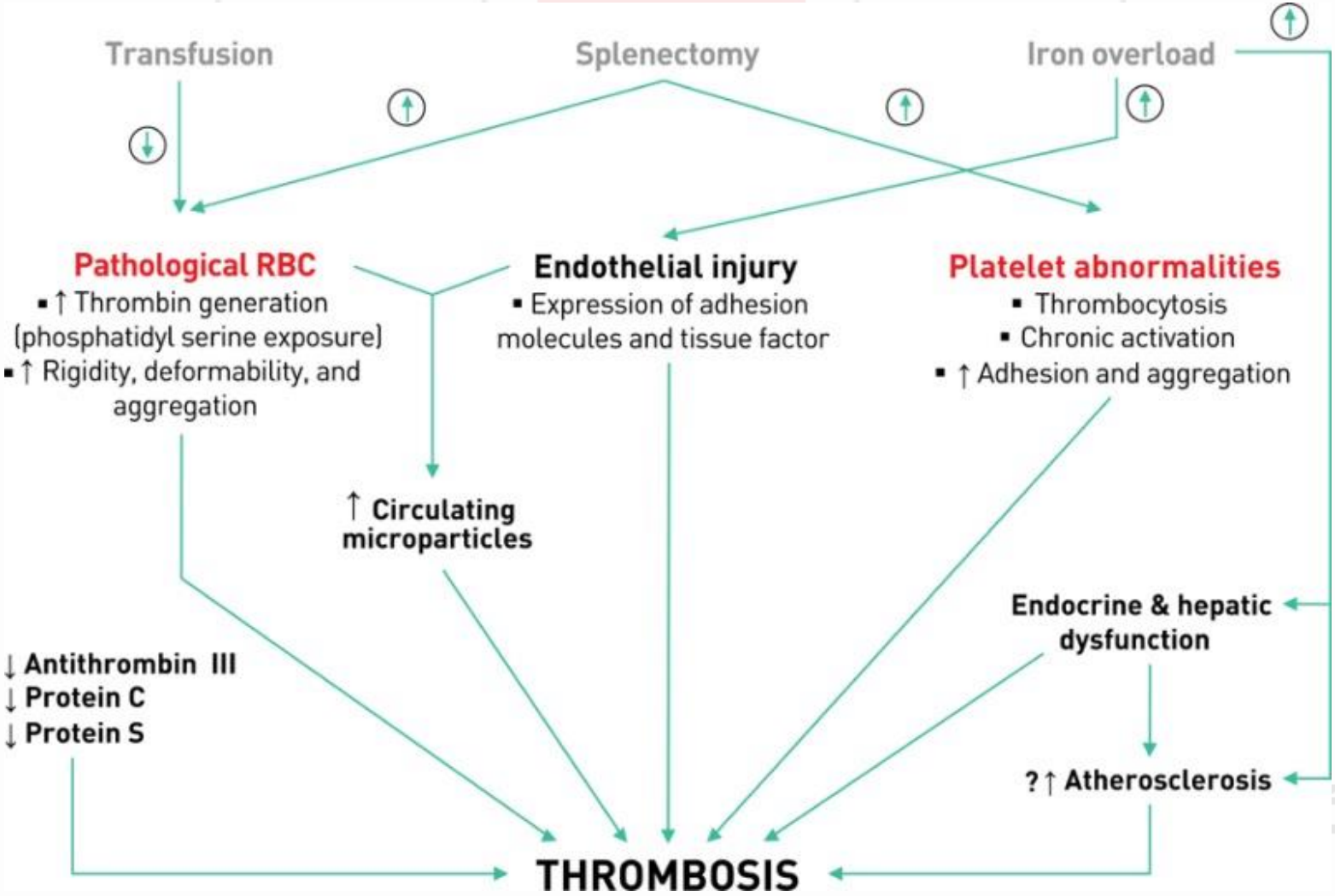


Haidar R, Mhaidli H, Taher AT. Paraspinal extramedullary hematopoiesis in patients with thalassemia intermedia. Eur Spine J. 2010;19(6):871–878

Thromboembolic events

- β-thalassemia major(~ 4%) and β-thalassemia intermedia (~ 9.6%-29%)
- 14% of mortalities in Thalassemia are due to TE
- The OPTIMAL CARE study: main independent risk factors for TE were:
  - Splenectomy: especially when high nucleated red blood cell (≥300 × 10^6/l) and platelet counts (≥500 × 10^9/l)
  - Age >35 year,
  - Iron overload (serum ferritin level ≥1000 ng/ml); (liver iron concentration ≥5 mg Fe/g dry weight or serum ferritin level ≥800 ng/ml)
  - Hemoglobin level <9 g/dl
- thrombotic events primarily occur in the venous system:
  - comprising deep vein thrombosis (DVT) (40%)
  - portal vein thrombosis (19%)
  - stroke (9%); silent ischemic lesions (26.7%)
  - Pulmonary embolism (12%)
  - others (20%)

Hypercoagulable state in Thalassemia



High risk patients

1. Patients with a diagnosis of β-thalassemia intermedia
2. Adult patients
3. Splenectomized patients
4. Never or previously minimally transfused patients
5. Patients with elevated platelet counts (≥500 × 10^9/l)
6. Patients with elevated nucleated red blood cell counts (≥300 × 10^6/l)
7. Patients with a hemoglobin level <9 g/dl
8. Patients with a history of pulmonary hypertension
9. Patients with iron overload (liver iron concentration ≥5 mg Fe/g dry weight or serum ferritin level ≥800 ng/ml)
10. Pregnant patients
11. Patients with a personal or family history of thrombosis

TE: management

- Transfusion
- Iron chelation
- Hydroxyurea:
  - reducing phospholipid expression on the surface of red blood cells
  - decreasing the white blood cell count and particularly monocytes that express tissue factor
- Anticoagulation therapy & Anti-platelet therapy

Recommendation:

- Close observation and Assessment with brain or cerebrovascular imaging
- Not yet , routine assessment or management of positive findings in asymptomatic patients
- Transfusion therapy (but NOT routine with no other indication use of iron chelation or hydroxyurea therapy) for the primary or secondary prevention TE in high-risk patients
- Treatment as per standard local or international guidelines
- Aspirin therapy should be considered in splenectomized NTDT patients with elevated platelet counts ($\geq 500 \times 10^9/l$)

risks of infections in TDT

- THERAPY RELATED FACTORS
  - Allogeneic blood transfusions
    - - Transfusion transmitted infections
    - - Transfusion related immune modulation
    - - Iron overload
  - Splenectomy
  - Iron chelation therapy
  - Central venous catheters
  - Stem cell transplantation
- DISEASE RELATED FACTORS
  - Ineffective erythropoiesis
  - Haemolysis
  - Anemia

Pathogens isolated from infections in thalassaemia patients

Pathogen	Number of cases (%)
Staphylococcus aureus	9 (15%)
Staphylococcus pneumonia	8 (13%)
Escherichia coli	7 (11%)
Klebsiella pneumonia	6 (10%)
Salmonella sp.	4 (7%)
Pseudomonas aeruginosa	3 (5%)
Brucella sp.	3 (5%)
Giardia lamblia	3 (5%)
Haemophilus influenzae	3 (5%)
Group A Streptococcus	3 (5%)
Campylobacter jejuni	2 (3%)
Gram negative bacteria	8 (13%)
Others	2 (3%)

From: Rahav G et al. Br J Haematol. 2006; 133(6)

Transfusion related bacterial sepsis in TM

- High fever, rigors and hypotension, beginning during or shortly after the transfusion
- Most often due to a Gram -negative bacilli - mainly Yersinia enterocolitica and Serratia marcescans. (Lindholm 2011).
- If bacterial contamination & sepsis is suspected :
  - Transfusion should be halted immediately.
  - Intravenous infusion of:
    - Third generation cephalosporin (cefotaxime 2 g every 8 h or ceftriaxone 2 g every 12 h) or Carbapenem (meropenem or imipenem 2 g every 8 h) combined with vancomycin (1–1.5 g every 12 h).
- • Gram's stain and blood culture are obtained from both
- Transfusion of pRBC units stored less than 2 weeks reduces the risk of transfusion associated Yersinia septicemia

Iron overload related Infections

- All groups of Pathogen protozoa, fungi, gram positive and negative bacteria require iron for survival and replication,(with the only exception being pathogenic Borrelia burgdorferi which use manganese in placeof iron.)
- Increase virulence and pathogenicity in the presence of excess iron: Some pathogens such as Yersinia enterocolitica, Klebsiella species, Escherichia coli, Streptococcus pneumonia Pseudomonas aeruginosa, Listeria monocytogenes, and Legionella pneumophila *(Weinberg 2000)* Also in in Candida albicans and Aspergillum fumigates
- increases the risk of viral infections *(Weinberg, 2009)*

- temporary discontinuation of DFO during a febrile illness until establishing whether the episode is caused by a pathogen that can use DFO as siderophore or taken under control is strongly advised (B)

- DFX or DFP can be continued during febrile episodes (C)

Overwhelming post-splenectomy infection (OPSI)

- Fulminating sepsis, meningitides or pneumonia triggered mainly by S. pneumonia followed by H. influenza type B and N.meningitides.
- Following brief prodromal symptoms such as fever, shivering, myalgia, vomiting, diarrhoea, and headache, septic shock develops in just a few hours
- Mortality rate is around 50 to 70% and most death occurs within the first 24 hours
- In patients at risk and with indicative symptoms, prompt initiation of empirical antibiotics is essential.
  - Intravenous infusion of third generation cephalosporin (cefotaxime 2 g every 8 h or ceftriaxone 2 g every 12 h), combined with gentamicin (5–7 mg/kg every 24h) or
  - ciprofloxacin (400 mg every 12 h) or
  - vancomycin (1–1.5 g every 12 h)

Ineffective erythropoesis and hemolysis related infections

- The increased phagocytic activity resulting from clearance of defective erythrocytes may reduce the capacity of the phagocytic system to defend against microorganisms : risk factor for bacterial infections

Yersinia

- **Pathophysiology:**
  - **Makes no siderophores of its own and therefore lives most efficiently in an iron-rich environment**
    - **unchelated patients with thalassaemia or**
    - **uses the DFO in chelating patients which is a siderophore**
- **Transmission:**
  - **Most commonly by the ingestion of contaminated food, meat, milk or water,**
  - **also be transmitted through blood: can survive and multiply in 4° ;**
- **Presentation:**
  - **Fever is the most common presenting feature, mostly low grade**
  - **Diarrhea, may be bloody in severe cases**
  - **Nausea and Vomiting**
  - **often associated with abdominal pain (mimics acute abdomen)**
  - **Extra gastrointestinal manifestations, such as arthralgia and skin rashes (mainly Erythema Nodusom), are sometimes seen.**
- **Complications :**
    - **Septicemia: mortality>50%**
    - **Abdominal: abscess (right iliac fossa), Splenic abscess,intussuception**
    - **Other: Nephritis; meningitis,**Pharyngitis- tonsillitis, acute respiratory distress syndrome

Yersinia: continue

- **Diagnosis:**
  - Stool Exam(wbc) & stool culture is the best diagnostic method
- **Management:**
  - Supportive care &Hydration
  - Isolation and Hand washing
  - Close observe and admission : Immune compromised, Iron Overloaded TM, TM on DFO,DM,
  - Ab therapy :Generally antibiotics are continued for at least two weeks after proven infection.:
    - Intravenous trimethoprim-sulfamethoxazole (400 mg sulfamethoxazole every 12 h) for 7 days (14 days in the case of septicemia) plus gentamicin (5–7 mg/kg every 24 h)
    - IM/IV ceftriaxone (2 g every 12 h) is an alternative in focal infections (e.g., enteritis, pharyngitis, tonsillitis).
    - Ciproflaxacin (400 mg every 12 h) is also an active antibiotic (A).
  - Iron chelation should not be restarted until the patient has been asymptomatic for over a week.
  - Relapse after restarting desferrioxamine:
  - a longer period of oral antibiotics may be necessary to eradicate the infection. Iron chelation can be recommenced after the infection has been eliminated.

Klebsiella

- Infection is presented with sinusitis, intracranial infections, septicemia and pyogenic abscesses
- Treatment:
- Stop DFO chelation
- Obtain suitable laboratory samples.
- Commence effective antibiotic treatment immediately.
  - Ceftazidime (2 gram every 8 h) plus gentamicin (5–7 mg/kg every 24 h) should be used for
  - treatment.
  - Meropenem, imipenem and fluoroquinolones are alternative antibiotics for resistant species.
- Early surgical intervention should be considered (A).

Increased transfusion requirements

Causes:

- Hypersplenism
- Alloantibody
  - Anti-E, anti-C and anti-Kell(85-90%)
  - Undetectable on pre-TX testing;rapidly rise within 2-10 days
- Autoantibody:
  - frequently in patients beginning transfusion therapy later in life
  - Steroids,immunosuppressive drugs and IVIG used but with little benefit
- Infection with HPV-B19 virus
  - an acute, life-threatening red cell aplasia, commonly referred to as “transient aplastic crisis”
  - other clinical problems such as myocarditis
- Bleeding
- Folate deficiency
- G6PD deficiency

Work-up :

- Acute vs Chronic
- Ab screening(IDC)
- Direct coombs
- Close observation of spleen size
- R/O autoimmune disorders
- HPV-B19 ;
  - IgM(7 days to months)
  - IgG(14 days to life long)
  - PCR

FEVER

Causes:

- Gram Positive encapsulated bacteria
- Yersinia
- Klebsiella
- Other: mucormycosis
- HTR
- Transfusion related bacterial sepsis
- Delayed transfusion reaction:
  - 2-10 days after TX
  - Mild fever
  - Mild unconjugated Bil
  - Spherocytosis
  - IDC positive

Work-up :

- Splenectomized or not
- Iron overloaded patients
- Deferoxamine
- Relapsing after restart DFO
- GI & Extra GI signs
- Asses the common foci of infection(renal,URT,PNSs,cholesyst,..): imaging ,culture,etc.
- Ab screening

Management:

- Treat swiftly and aggressively
- Stop IC therapy until definite the cause
- Start Abs:
  - Penicilins
  - Ciprofloxacillin
  - cotrimoxazole

Diarrhea, Nausea &Vomiting

- Yersinia
- Drug related: DFP ; DFX
  - DFP: occur early in therapy in about one-third of patients dose-dependent
  - DFX: dose dependent
  - mostly mild to moderate,
  - generally transient,
  - mostly resolve even if treatment is continued
  - usually resolve without specific intervention
    - Antacids (Except for DFX which is contraindicated), antiemetics will generally reduce symptoms.
    - taking L1 with food may help reduce nausea.

Skin rash

- Drug related: DFP;DFX
  - dose-dependent
  - mostly mild to moderate,
  - generally transient,
  - mostly resolve even if treatment is continued
  - Patients with severe rash may require interruption of treatment. reintroduction may be conducted in combination with a short period of oral steroid administration
- DFO
  - Local skin reactions, such as itching, erythema
  - Ulceration at the site of a recent infusion results from an intradermal infusion
- Transfusion reactions: urticaria , pruritus
- Yersinia : Erythema Nodusom (2-20 day after fever)

Back Pain

Causes;

- Osteoporosis and microfractures
- Prolapse in disc:
  - More commonly in lower thoracic and upper lumbar
- End plate degeneration
- General causes:
  - congenital anomalies of the lumbar spine (spondylolysis, spondylolisthesis),
  - trauma with sprains and strains,

- Acute vs chronic
- Exclude neurological deficit: weakness,numbness,bowel or voiding problems
- Consider cord compression
- Spinal X-ray and MRI
- Brain CT(with contrast if creatinin permits)
- LP (if CT non-conclusiive)

With Focal Neurological Symptoms eg. weakness, numbness, bowel or voiding abnormalities

NO

Low threshold for imaging (X-ray, MRI)
? Osteoporosis related fracture
? Extramedullary erythropoiesis

YES

Go to previous chart "Focal Neurological Defict"

FOCAL NEUROLOGICAL DEFICIT

Upper Motor Neurone (UMN)

UMN?

ECG YES

Cerebral process?
- ? Stroke
  - Trombotic/embolic
  - Bleed
- Abscess
- Tumour

NO

Spinal cord lesions?
- ? Extamedullary erythropoiesis
- ? Spinal vessel thrombosis

Consult neurologist Urgent MRI

MRI if rapidly available (<1h). CT brain (no contrast). Consider IV contrast concommitantly if not contraindicated eg. raised creatinine

LP while awaiting creatinine

LP if CT without/with contrast is non conclusive: consult neuro

Unexplained Abdominal Pain

- Cholelythiasis
  - two-thirds of which have multiple calcified bilirubin stones by the age of 15.
  - true episodes of cholecystitis or cholangitis are rare
- Pancreatitis
  - 3 to 7 percent with gallstone
- Portal vein thrombosis(especially after splenectomy)
  - acutely with symptoms of an acute abdomen, particularly in adolescents,
  - asymptomatic for long periods of time until symptoms reflecting chronic vascularobstruction (portal hypertension) occur
- Renal stones:
  - Due to hypercalcuria/hyperuricosuria

Continue:

- Congestive cardiac failure:
  - Consider augmented ICT(high dose DFO/ DFO+DFP) unless contraindicated(yersinia;allergy to DFO,etc)
- Yersinia:*
- Hepatic capsule distension:
  - extramedullary erythropoiesis in children
  - hepatomegaly becomes fixed and non-reducible by blood transfusion, due to development of cirrhosis secondary to increased iron deposition

Chest Pain

- Pericarditis and myocarditis:
  - T2* MRI,Echo,ECG
- Rib microfracture (extramedullary expansion)
  - Palpate chest wall; pain on gentel pressure
- Pulmonary embolism:
  - D-dimer, High resolution CT, Perfusion Scan
- Acute coronary syndrome

Dyspnea

- Dysrhythmia:
  - Symptoms include palpitations, syncopes, shortness of breath, epigastric pain, decreased exercise tolerance and peripheral edema
  - 24H ECG monitoring
  - Supraventricular: more commom, reassurance
  - Ventricular:less common, more sever ,warning
  - Intensive chelation treatment has been demonstrated to reduce arrhythmias.
- Rib microfracture
- Transfusion adverse events: TACO ;TRALI; alleric reactions; AHTR; Delayed Transfusion reaction

continue

- Pump failure
- Pulmonary embolism
- Pulmonary hypertension:
  - prevalent in patients with TI (59.1%)
  - Mechanism:endothelial dysfunctionwith increased inflammation and apoptosis,decreased nitric oxide and nitric oxidesynthase production, pulmonaryhaemosiderosis and local thrombosis.
  - Management:
    - regular TX, ICTindicated in TI patients according to the early detection of PHT indices.
    - Sildenafil

Leg cramps

One-third of patients with thalassaemia major suffer from leg cramps, muscle wasting and weakness:

- Hypocalcaemia
- Hypoparathyroidism
- neuromuscular and vascular issues

arthralgia

- Drug related:
  - DFP:
    - varies widely across studies(4-40%), perhaps due to different degrees of iron overload
    - not confined to the first year of therapy
    - May require the reduction or temporary interruption if not responded to NSAIDS
  - DFP
- Hypoparathyroidism
- Yersinia

Worsening jaundice

- Gilberts
  - The most common inherited disorder of bilirubin glucuronidation
  - is usually diagnosed in young adults who present with mild, predominantly unconjugated when alterations in sex steroid concentrations affect bilirubin metabolism
  - Thalassaemia patients with inherited Gilbert's syndrome are at increased risk for haemolysis
- Increased haemolysis
- Drug Reaction
- Liver failure

مجلس تمام گشت و به آخر رسید عمر
ما همچنان در اول وصف تو مانده ایم