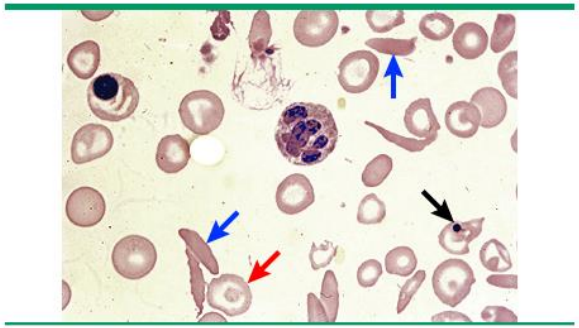
SHORT CASES RESPIRATORY COMPLICATIONS OF SICKLE CELL DISEASE

Marie-Christine Hendriks
PGY 5 Pediatric Respirology
CHU Sainte-Justine

SICKLE CELL DISEASE 101

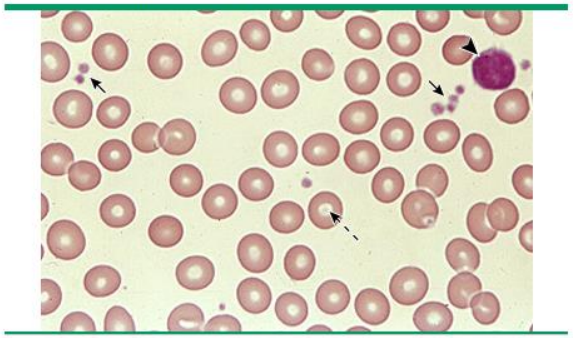
- Hemoglobinopathy (AR)
  - Amino acid substitution in the beta globin chain of hemoglobin = HbS
  - Hb S is poorly soluble when deoxygenated
  - Hypoxia -> HbS polymerizes -> distortion of red cells into crescent-> obstruction of vessels
  - Complications 2nd to vaso-occlusive phenomena or hemolysis

Peripheral blood smear in sickle cell anemia



Peripheral blood smear from a patient with sickle cell anemia. This smear shows multiple sickle cells (blue arrows). There are also

Normal peripheral blood smear



High-power view of a normal peripheral blood smear. Several platelets (arrows) and a normal lymphocyte (arrowhead) can also

SICKLE CELL DISEASE 101

- 8-10 % of African Americans have sickle cell trait (HbAS)
- 1:2647 children
- 1:400 African American children
- At risk populations
  - Africans, Mediterranean, Middle East, Indians, Caribbean, Latinos
- Newborn screening
- Dx = hemoglobin electrophoresis

Kliegman et all, «Nelson Textbook of Pediatrics», 19e edition.

SICKLE CELL DISEASE 101

TABLEAU 25.1 | Profils hématologiques des différents phénotypes d'anémie falciforme

Phénotype	SS	Sβ^0-thalassémie	SC	Sβ$^+$-thalassémie	AS
Hb (g/L) (50^e percentile)	85	85	105	110	N
Volume globulaire moyen	N	↓↓	↓	↓	N

N : normal ; ↓ : diminué ; ↓↓ : très diminué

Robitaille Nancy et Chevalier Isabelle, «Anémie falciforme (drépanocytose)», Dictionnaire de pédiatrie Weber, 3e édition, p.127-131

SICKLE CELL DISEASE 101

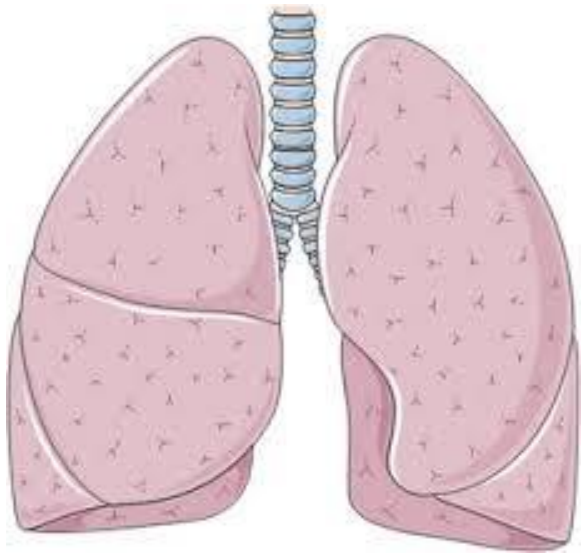
- Clinical manifestations
  - Functional asplenia
    - Increased risk of infection by encapsulated bacteria
    - Salmonella typhi osteomyelitis
  - Vaso-occlusive crisis
  - Splenic sequestration
  - Stroke
  - Aplastic crisis
  - Renal complications
  - Other complications

SICKLE CELL DISEASE 101

- Multidisciplinary team
- Folic acid
- Prophylactic antibiotic
- Hydroxyurea
- Blood transfusions
- Hematopoietic cell transplantation

SICKLE CELL DISEASE 101

- Acute and chronic respiratory complications are frequent
- They contribute to morbidity and mortality



CASE #1

- 6-year-old girl
- Previous medical history
  - Born in Quebec
  - Sickle cell disease, Hb SS (Hb 85-90)
  - Multiple vaso-occlusive crisis
  - 1 previous acute chest syndrome in 2015
  - 3 previous transfusions (last 09/2016)
  - Last echocardiogram 06/2016 normal
- Family medical history
  - Parents sickle cell trait
- Rx: folic acid, hydroxyurea

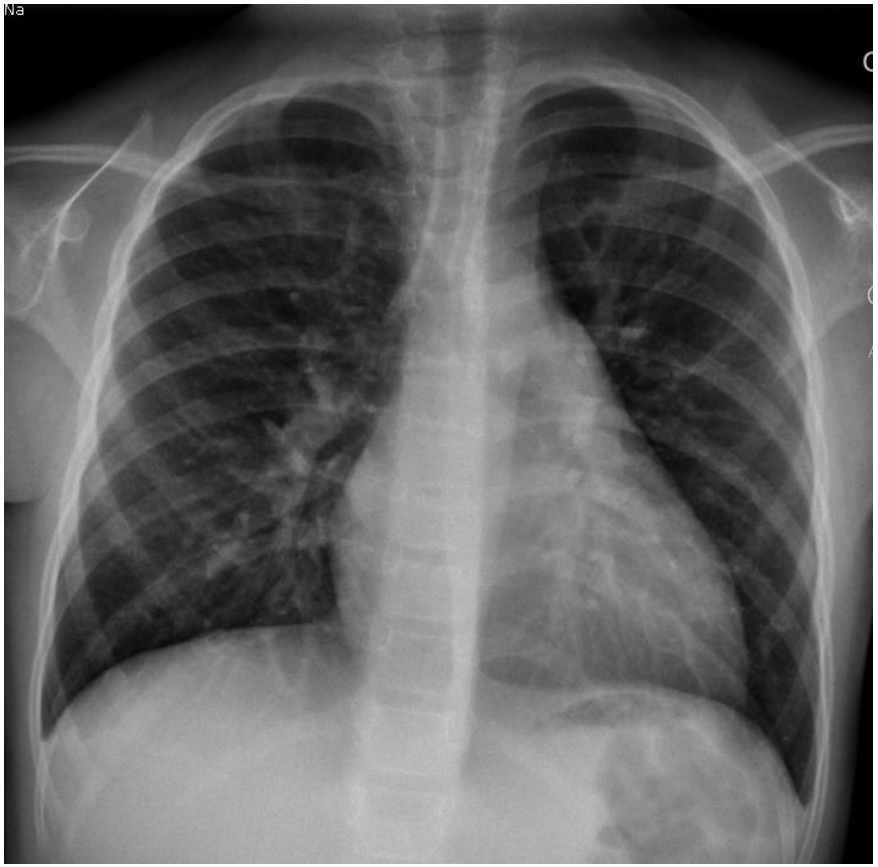
CASE #1

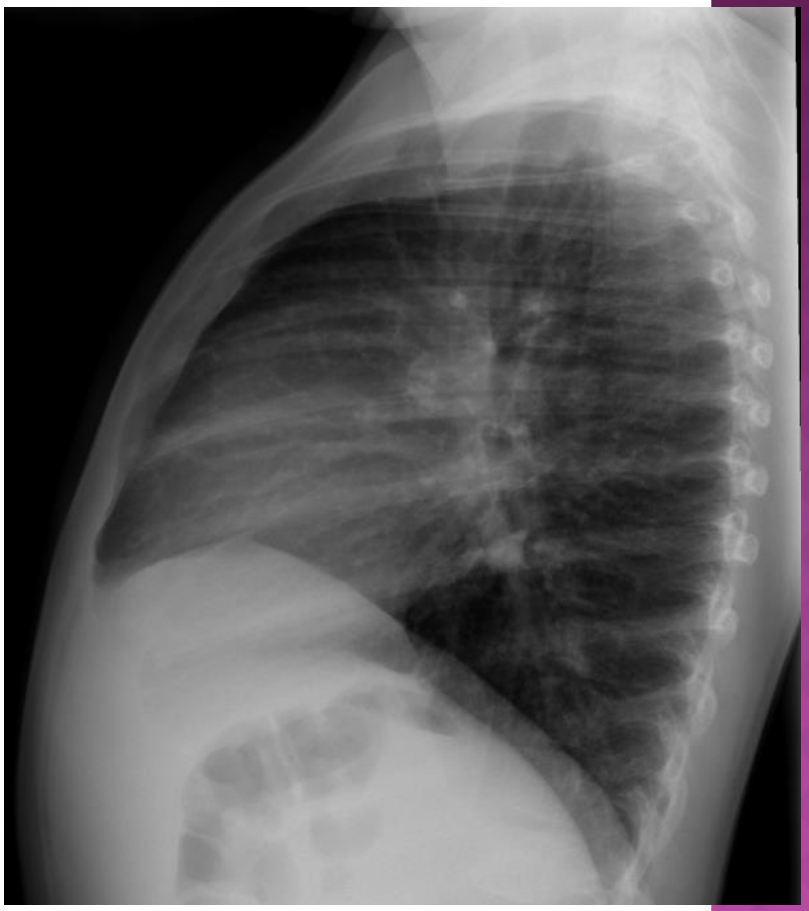
- Admitted for vaso-occlusive crisis + fever
  - Morphine 0.1 mg/kg q3h
  - Hydration
  - Ceftriaxone
- Day 2
  - Morphine 0.15 mg/kg q3h -> morphine perfusion 0.08 mg/kg/h
  - Blood cultures negative

CASE #1

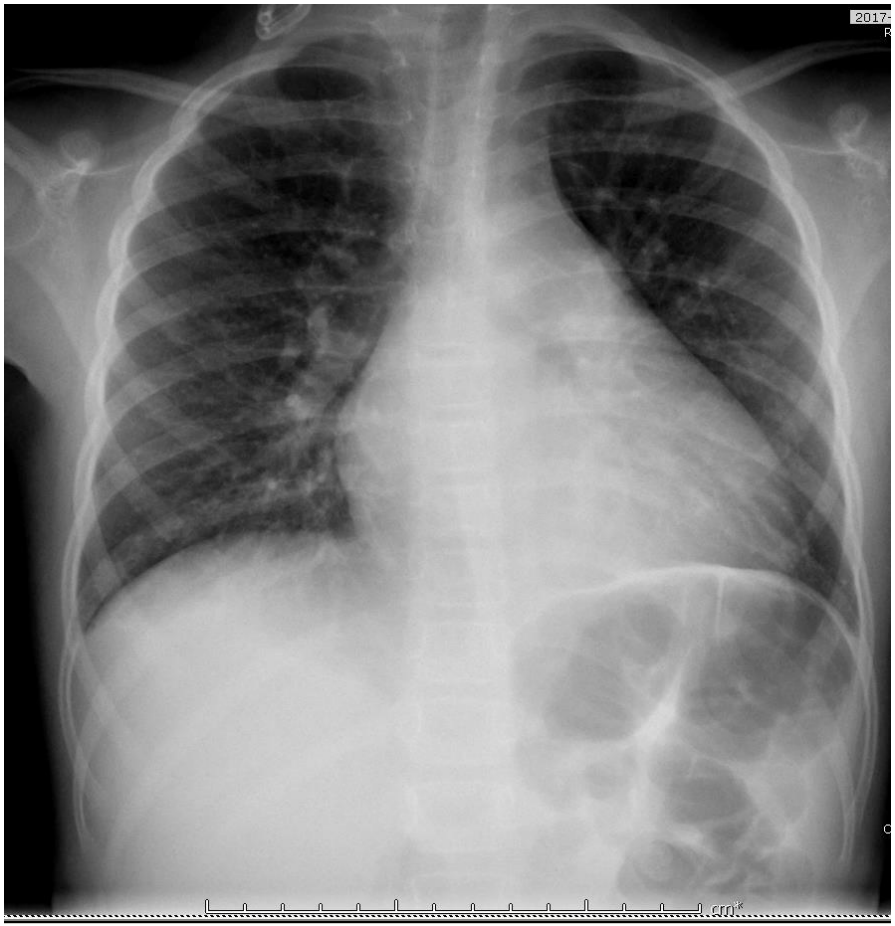
- Day 3
  - Desaturation 85%, which required 0.5L of oxygen
  - New cough
  - No respiratory distress
  - Bilateral crackles at bases and bronchial breath sounds on left base on exam

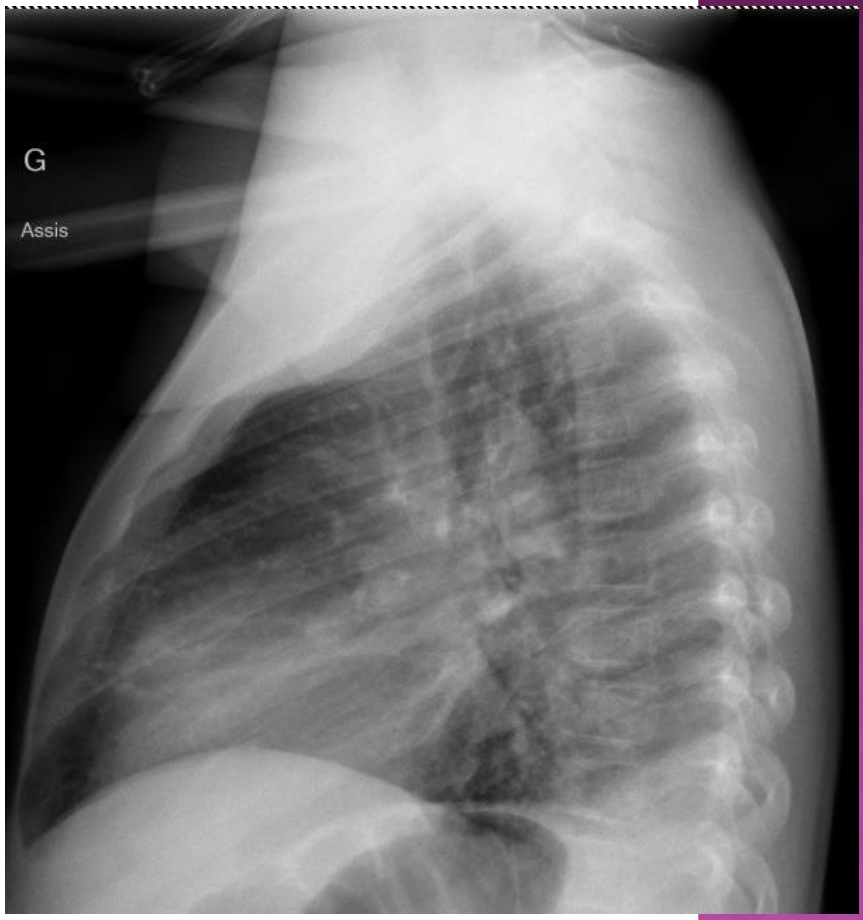
CASE #1 - ADMISSION





CASE #1 - DAY 3





CASE #1

- Acute chest syndrome with left lower lobe opacity on chest X-ray
  - Cefotaxime + clarithromycin
  - Respiratory physiotherapy
  - Monitoring
  - Transfusion

CASE #1

- What is the definition of acute chest syndrome?
- What were the possible etiologies for this patient?
- What is the management of acute chest syndrome?

ACUTE CHEST SYNDROME

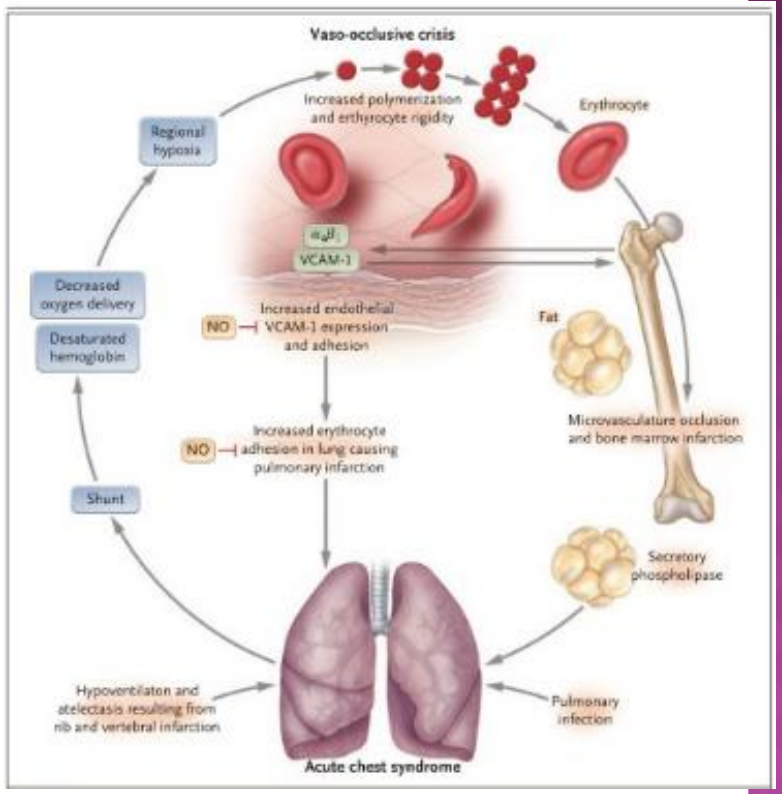
- Most common acute respiratory complication
- 2nd cause of hospitalization
- 1st cause of death
- 50% of HbSS patients will have at least 1 episode
- Peak incidence 2-4 years old
- 50% of patients were initially hospitalized for another reason, most frequently a vaso-occlusive crisis

ACUTE CHEST SYNDROME

- Definition
  - New pulmonary infiltrate on chest X-ray involving at least one lung segment and not consistent with atelectasis
  - At least one
    - Chest pain
    - Fever > 38.5
    - Tachypnea, wheezing, cough, increased work of breathing
    - Hypoxemia

ACUTE CHEST SYNDROME

- Pathogenesis is complex
- Multiple possible etiologies
  - Atelectasis
  - Pulmonary edema
  - Bronchospasm
  - Vaso-occlusive crisis
  - Excessive administration of opioid
  - Pneumonia/infection
  - Fat embolus
  - Thromboembolism



Gladwin et all, «Pulmonary complications of Sickle Cell Disease», NEJM, nov 2008.

ACUTE CHEST SYNDROME

- National Acute Chest Syndrome Study Group

CAUSES AND OUTCOMES OF THE ACUTE CHEST SYNDROME IN SICKLE CELL DISEASE

ELLIOTT P. VICHINSKY, M.D., LYNNE D. NEUMAYR, M.D., ANN N. EARLES, R.N., P.N.P., ROGER WILLIAMS, M.D., EVELYNE T. LENNETTE, PH.D., DEBORAH DEAN, M.D., M.P.H., BRUCE NICKERSON, M.D., EUGENE ORRINGER, M.D., VIRGIL MCKIE, M.D., RITA BELLEVUE, M.D., CHARLES DAESCHNER, M.D., AND ELIZABETH A. MANCI, M.D., FOR THE NATIONAL ACUTE CHEST SYNDROME STUDY GROUP*

- Multicenter prospective study
- Hb SS, SC ou SB thal
- Usual definition of acute chest syndrome
- 671 episodes 1993-1997

Vinchinsky et all, «Causes and Outcomes of the Acute Chest Syndrome in Sickle Cell Disease», NEJM, Juin 2000.

ACUTE CHEST SYNDROME

TABLE 4. CAUSES OF THE ACUTE CHEST SYNDROME.*

CAUSE	ALL EPISODES (N=670)	AGE AT EPISODE OF ACUTE CHEST SYNDROME		
		0–9 YR (N=329)	10–19 YR (N=188)	≥20 YR (N=153)
		no. of episodes (%)		
Fat embolism, with or without infection†	59 (8.8)	24	16	19
Chlamydia‡	48 (7.2)	19	15	14
Mycoplasma§	44 (6.6)	29	7	8
Virus	43 (6.4)	36	5	2
Bacteria	30 (4.5)	13	5	12
Mixed infections	25 (3.7)	16	6	3
Legionella	4 (0.6)	3	0	1
Miscellaneous infections¶	3 (0.4)	0	3	0
Infarction‖	108 (16.1)	50	43	15
Unknown**	306 (45.7)	139	88	79

Vinchinsky et all, «Causes and Outcomes of the Acute Chest Syndrome in Sickle Cell Disease», NEJM, Juin 2000.

ACUTE CHEST SYNDROME

- Management
  - Admission
  - Fluid
  - Analgesia
  - Oxygen for Sat >= 95%
  - Respiratory physiotherapy
  - Bronchodilators
  - Antibiotics
  - Fever control

ACUTE CHEST SYNDROME

CONSENSUS STATEMENT ON THE CARE OF PATIENTS WITH SICKLE CELL DISEASE IN CANADA

- Transfusions

- RBC transfusion in the setting of acute chest syndrome results in improved oxygenation.[17] Some studies have observed equivalent outcomes whether patients are treated with exchange transfusion (HbS% goal of 30%) or simple transfusion (Hb goal of 100 g/L).[18] Other studies have found, however, that patients receiving top-up transfusions may progress to requiring a full exchange.[19]
- In the absence of evidence from randomized controlled trials, most patients with acute chest syndrome should be transfused, with exchange transfusions reserved for patients with more severe or rapidly progressing disease.[20] Signs of severe disease include:
  - altered mental status
  - persistent heart rate >125 beats/minute, respiratory rate >30 breaths/minute, temperature >40°C, or worsening hypotension
  - arterial pH <7.35; peripheral capillary oxygen saturation (SpO2)% <88% despite aggressive ventilatory support
  - serial decline in SpO2% or alveolar-arterial gradient
  - fall in hemoglobin >20 g/L
  - platelet count <200/fL
  - elevated troponin or brain natriuretic peptide (BNP)
  - evidence of multiorgan failure (e.g., renal or hepatic dysfunction)
  - pleural effusions or progressive pulmonary infiltrates

Verhovsek et all, «Consensus Statement on the Care of Patients With Sickle Cell Disease in Canada», CanHeam Ottawa, 2015.

ACUTE CHEST SYNDROME

- Complications
  - Neurologic
  - Respiratory failure
  - Pulmonary infarction
  - Pulmonary fibrosis
  - Pulmonary hypertension
  - Unexpected death

ACUTE CHEST SYNDROME

- Prevention
  - Prophylactic antibiotic and vaccination
  - Pulmonary function tests and resting saturation
  - Aggressive treatment of asthmatic patients
  - Hydroxyurea
  - Transfusion therapy

CASE #2

- 15-year-old boy
- Admitted for hypoxemia
- Past medical history
  - Born at 35 weeks of gestation, in Boston
  - Sickle cell disease, HbSS (Hb 70)
  - No previous acute chest syndrome.
  - Last echocardiogram 2011 normal
  - Arnold Chiari type 1
  - Eczema
- Family medical history
  - Mother known for sickle cell disease

CASE #2

- No animals. No smoking.
- Lives with his mother.
- Immunization up to date.
- Rx: Folic acid
- Does not take his hydroxyurea because of nausea.

CASE #2

- Admitted for hypoxemia on a routine visit
- At last visit 3 months ago: SpO2 93%
- He now presents to the clinic for his PFT SpO2 is 86-87%
- He does not have acute symptoms
- Chronic dyspnea on exertion
- No improvement after Fluticasone 125 mcg BID for 3 months
- Snoring, fatigue, school difficulties

CASE #2

- RR 18 SpO2 91%
- No tonsillar hypertrophy
- Pulmonary exam normal
- Grade 2 systolic murmur. P2 N.
- Clubbing grade 1

CASE #2

- What is your differential diagnosis for this 15-year-old patient with sickle cell disease and hypoxemia?

HYPOXEMIA

- Saturation often decreased in sickle cell disease patients
  - Mean daytime saturation 94%, median 95%
  - 10% of asymptomatic patients have SpO2 < 90%
  - Measurements recommended at every visit

UONG et all, «Daytime pulse oximeter measurements do not predict incidence of pain and acute chest syndrome episodes in sickle cell anemia», J Pediatr. 2006;149(5):707.

Verhovsek et all, «Consensus Statement on the Care of Patients With Sickle Cell Disease in Canada», CanHeam Ottawa, 2015.

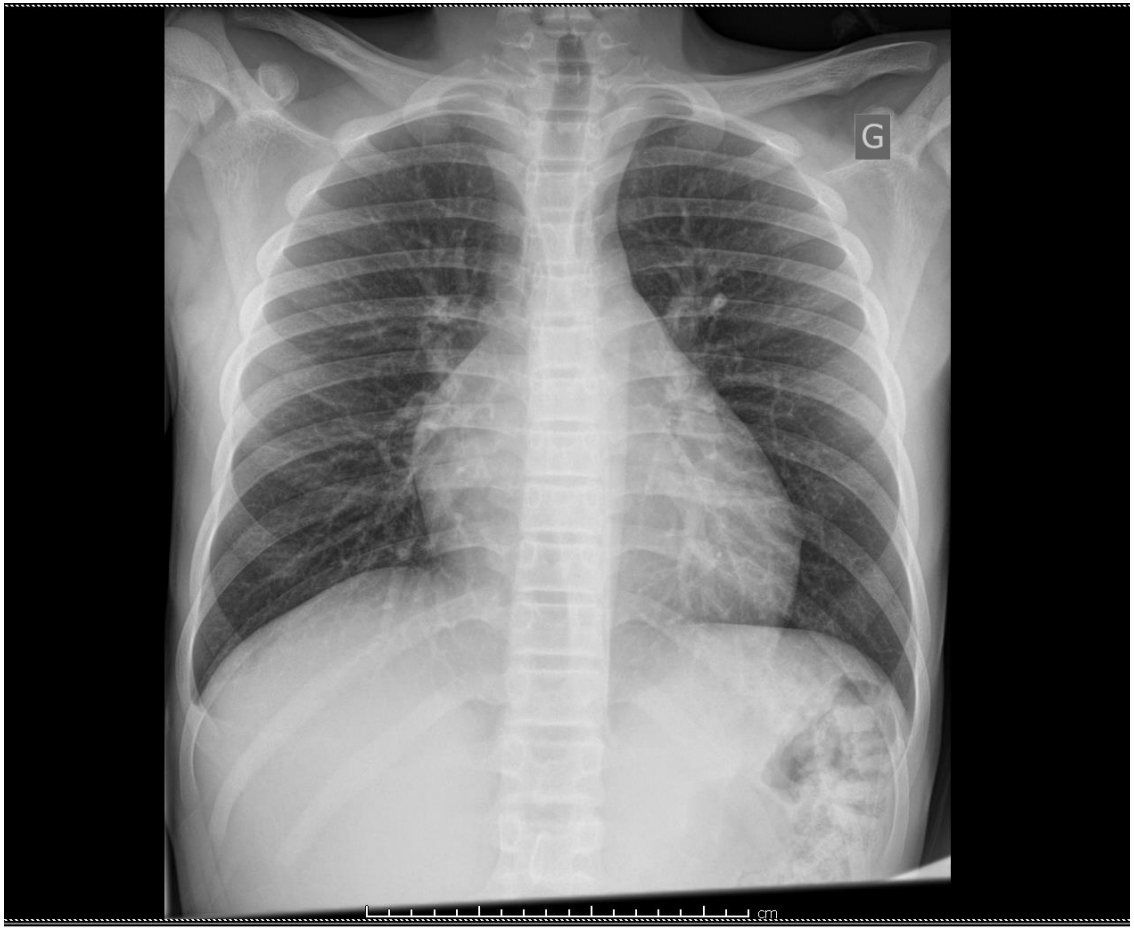
HYPOXEMIA – DIFFERENTIAL DIAGNOSIS

- Acute chest syndrome
- Pneumonia
- Pulmonary embolism
- Sepsis
- Asthma
- Pulmonary hypertension
- Thromboembolism
- Obstructive sleep apnea
- Lung infarctions
- Pulmonary fibrosis
- Cardiac dysfunction
- Low Hb F
- Elevated HbMeth

CASE #2

- What investigation do you want to do for this patient?

CASE #2



CASE #2

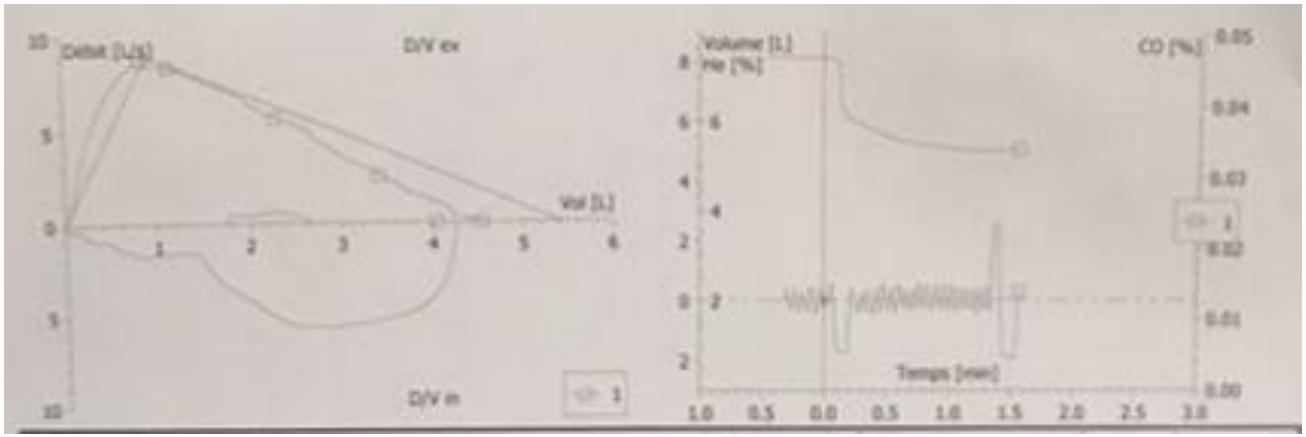
- Hb 61
- WBC normal
- pCO2 38

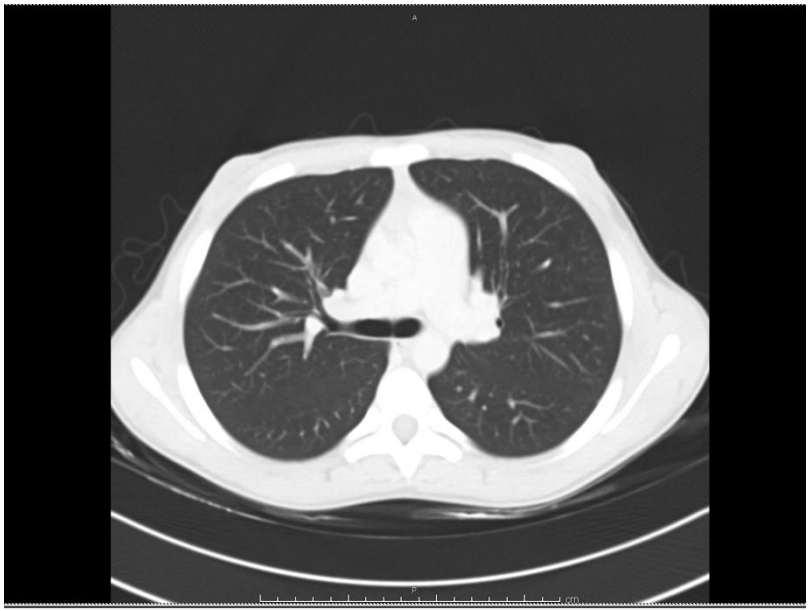
CASE #2

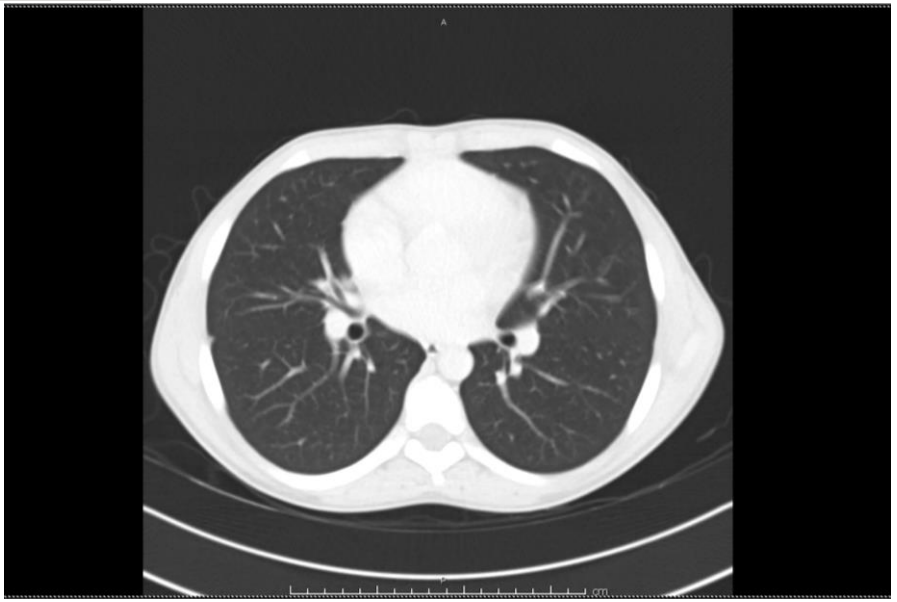
- Overnight oximetry
  - Mean SpO2 86.5%
  - Min SpO2 75%
  - 96% of time < 90%!

CASE #2

	Ref	Meas	%
FVC	5.42	4.54	83.6
FEV1	4.54	4.04	89.1
FEV1/FVC	85.24	89.14	
FEF 25-75%	4.67	4.72	101.1
CV	4.89	4.53	92.6
RV-He	1.26	1.34	106.1
RV/TLC	20.24	22.80	112.7
TLC-He	6.22	5.87	94.3
DLCOc	32.65	31.40	96.3



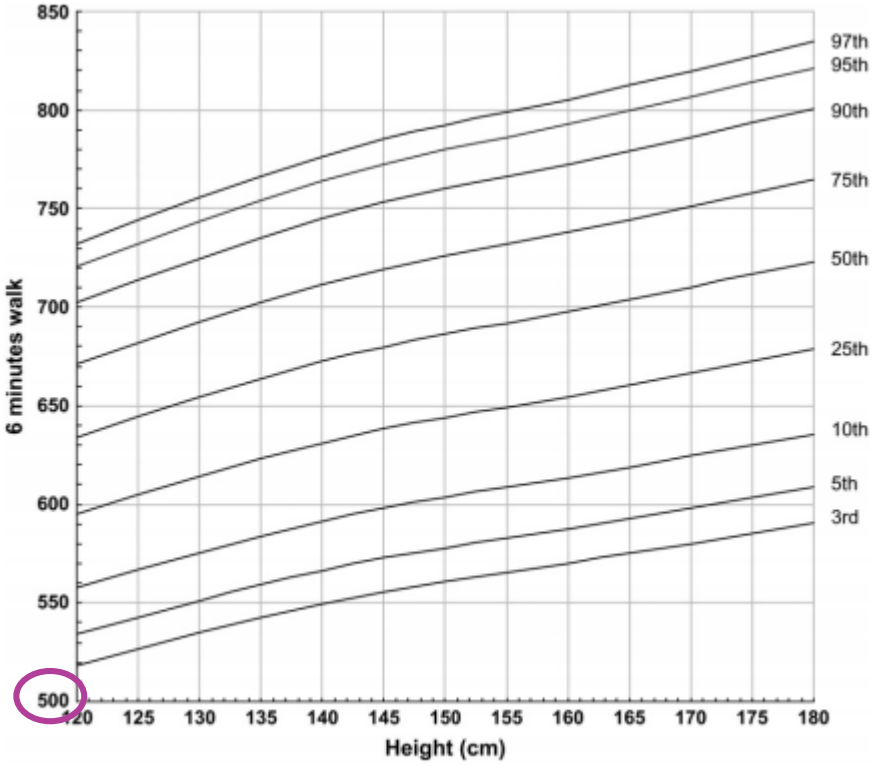




CASE #2

- V/Q scan normal
- ECG normal
- Echocardiography normal
- 6MWT:
  - SpO2 88-93%
  - Walked distance 360 m

Figure 1. Reference centile curves for six-minute-walk distances for males.



Li et al, Standard Reference for the Six Minute Walk Test in Healthy Children Aged 7 to 16 Years, American Journal of Respiratory and Critical Care Medicine, vol 176, 2007.

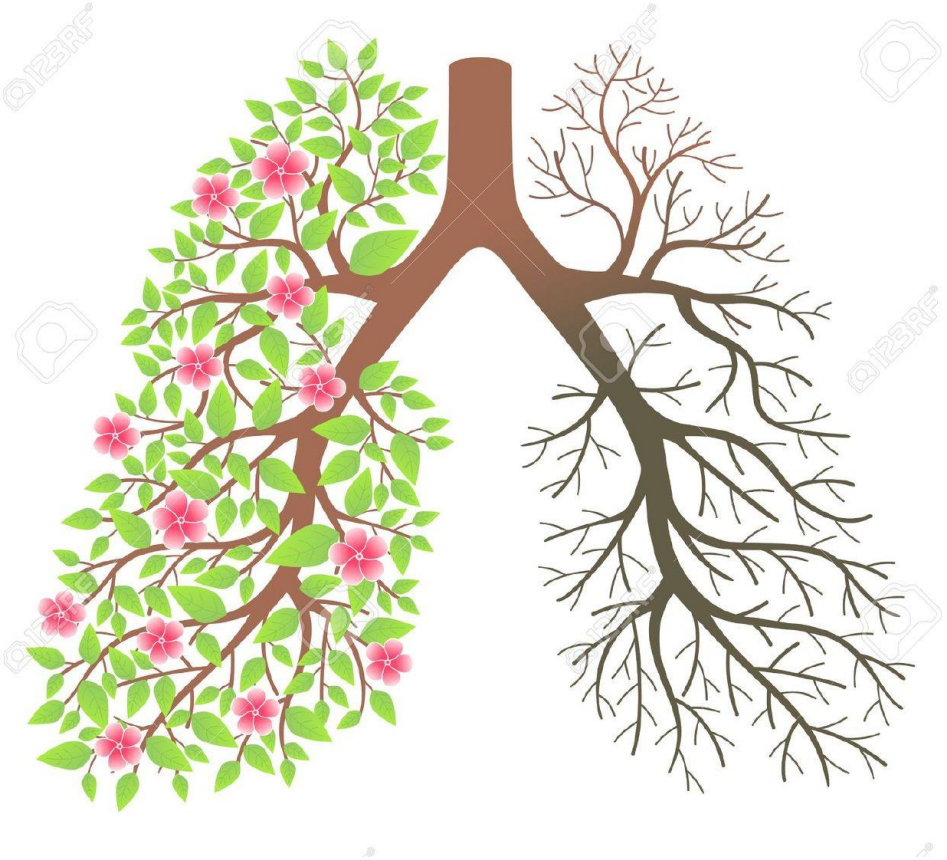
CASE #2

- Respiratory investigation normal
- Chronic low saturation because of poor adherence to hydroxyurea with low HbF
- Transfusion
- PSG
  - AHI 2 (0.65 obstructive, 1.35 central)
  - Mean SpO2 93%
  - 1.2% of time < 90%

CASE #2

- Conclusion: Chronic low saturation because of poor adherence to hydroxyurea with low HbF
- No oxygen therapy
- Close follow-up

CHRONIC RESPIRATORY COMPLICATIONS



CHRONIC DYSPNEA

- Common
- Often not reported
- Decreased exercise capacity that begins in adolescence
- Etiology often multi-factorial
  - Anemia
  - Deconditioning
  - Asthma
  - Pulmonary hypertension
  - Thromboembolism
  - Pulmonary fibrosis
  - Myocardial dysfunction

ASTHMA

- Relationship between sickle cell disease and asthma not well understood, but increased risk
  - Severe airway narrowing-> local hypoxia-> sickling and systemic inflammation?
  - Recurrent acute chest syndrome-> pulmonary inflammation-> increased airway reactivity?

ASTHMA

- Clinical manifestations similar to other pulmonary complications
- Demonstration of variable airflow obstruction
- Usual management
- Associated with increased incidence of acute chest syndrome and vaso-occlusive crisis

PULMONARY HYPERTENSION

- Severe complication
- 6-10% of adults
- 10-20% of children have increased TRV
- Independent risk factor of mortality in adults and morbidity in children
- Pathogenesis unknown but potential contributing factors implicated

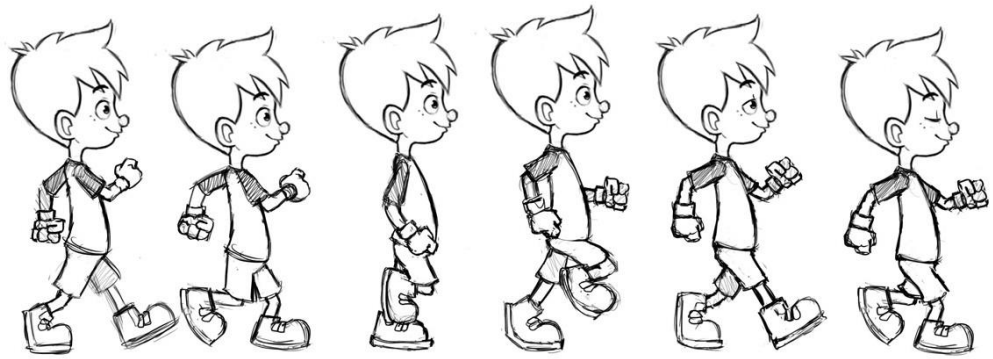
Uptodate, Pulmonary complications of sickle cell disease

PULMONARY HYPERTENSION

- Variable and non-specific clinical presentation
  - Dyspnea on exertion
  - Chest pain
  - Palpitations
  - Syncope/near-syncope
  - Decreased exercise capacity
  - Decreased activities without other reported symptom
  - Fatigue
- If symptoms: oximetry at rest and exertion

PULMONARY HYPERTENSION

- Investigation
  - Echocardiography
  - pro-BNP
  - Pulmonary function tests with diffusion
  - Six minute walk test
  - Definitive diagnosis: cardiac catheterization with PAP >= 25 mmHg



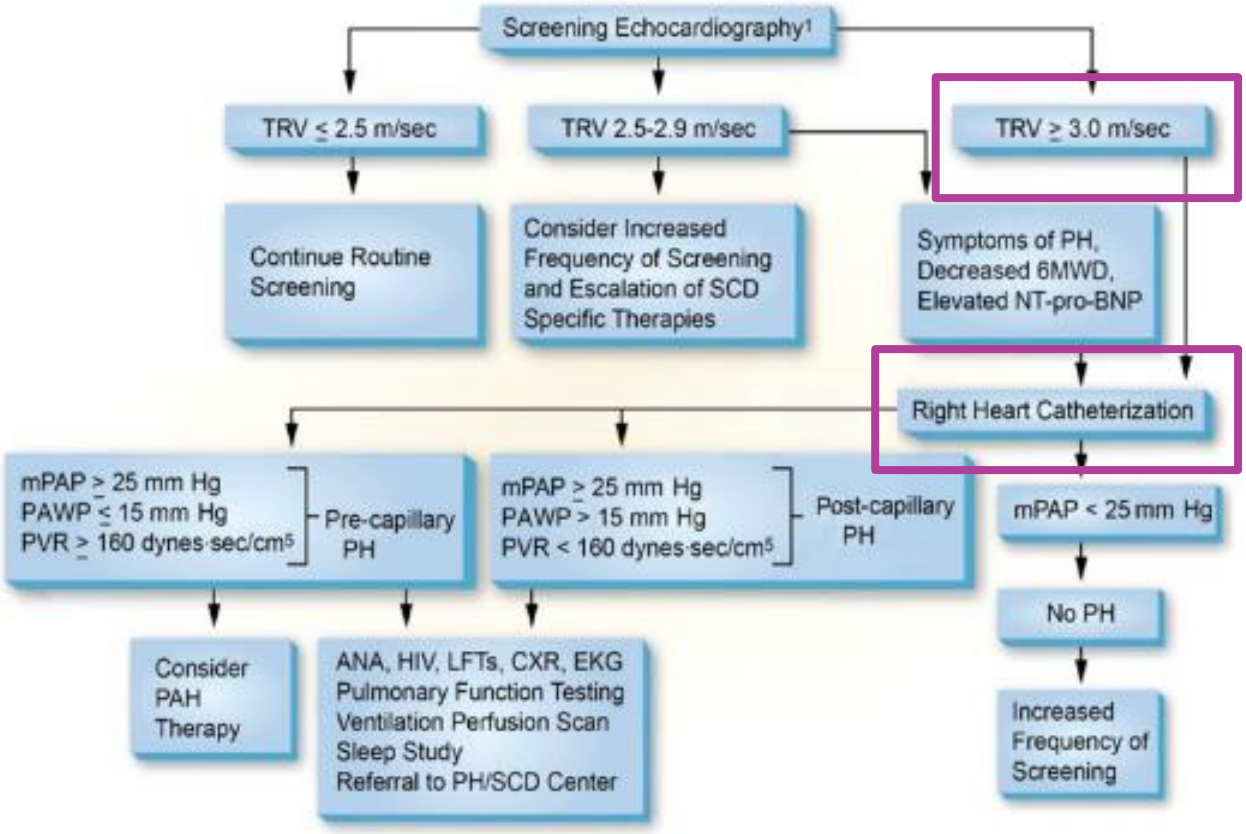
PULMONARY HYPERTENSION

- Echocardiography
  - Estimates PAP via TRV
    - PPV 25% in adults
    - >= 2.5 m/sec abnormal
    - >= 3 m/sec suggests moderate to severe pulmonary hypertension
  - Evaluates cardiac function, ventricular hypertrophy and dilatation
- Six minute walk test
  - Evaluates desaturation on exertion and walked distance
- Pro-BNP
  - Correlates with severity

Parent F et al, «A hemodynamic study of pulmonary hypertension in sickle cell disease», Nengl J Med. 2011;365(1):44

PULMONARY HYPERTENSION

AMERICAN THORACIC SOCIETY DOCUMENTS



Klings et all, «An Official American Thoracic Society Clinical Practice Guideline: Diagnosis, Risk Stratification, and Management of Pulmonary Hypertension of Sickle Cell Disease», nov 2013.

PULMONARY HYPERTENSION

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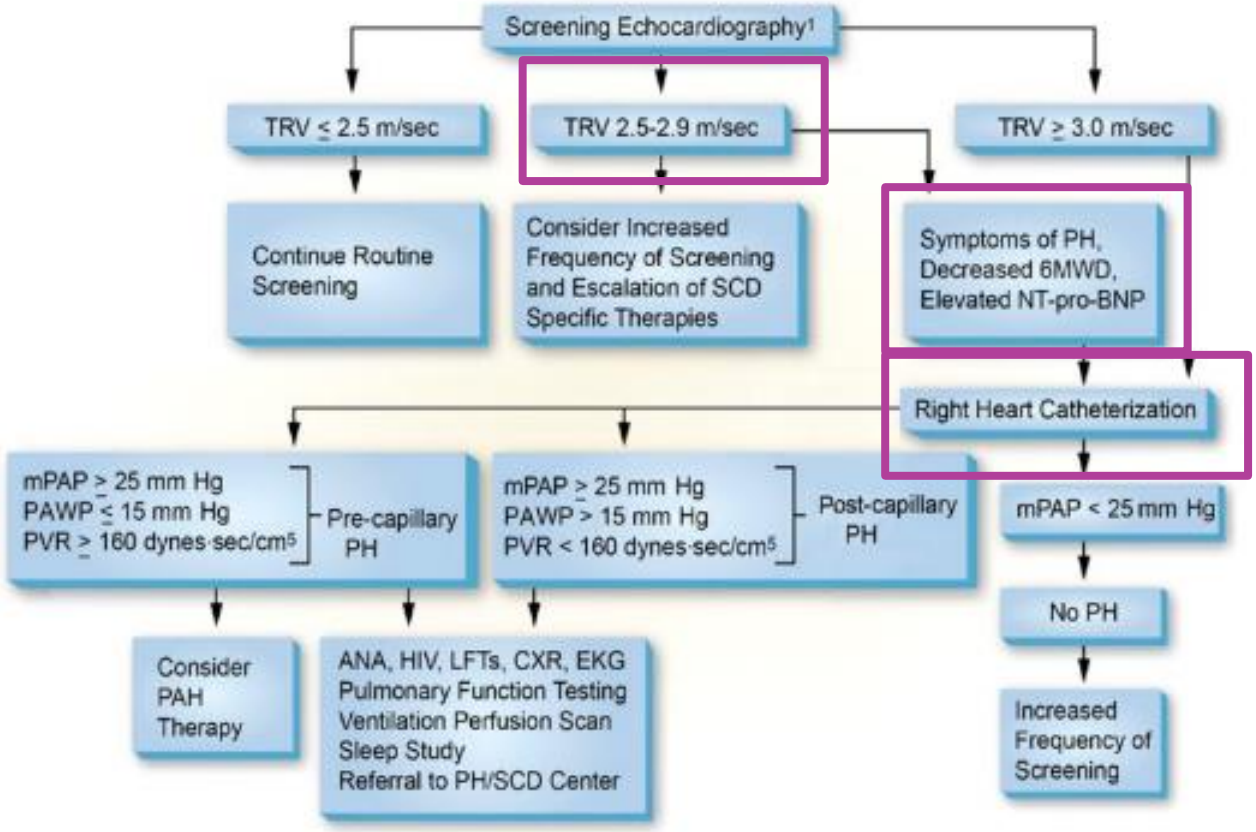

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PULMONARY HYPERTENSION

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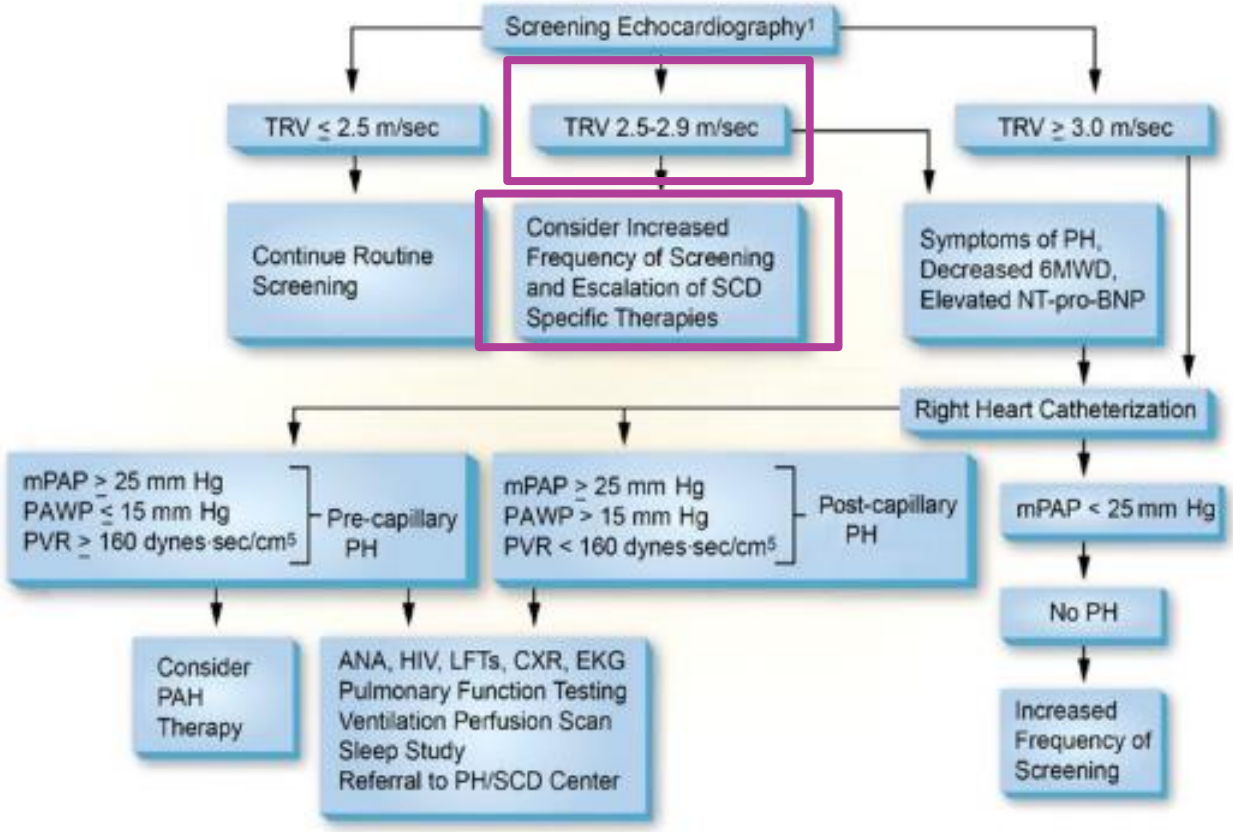

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PULMONARY HYPERTENSION

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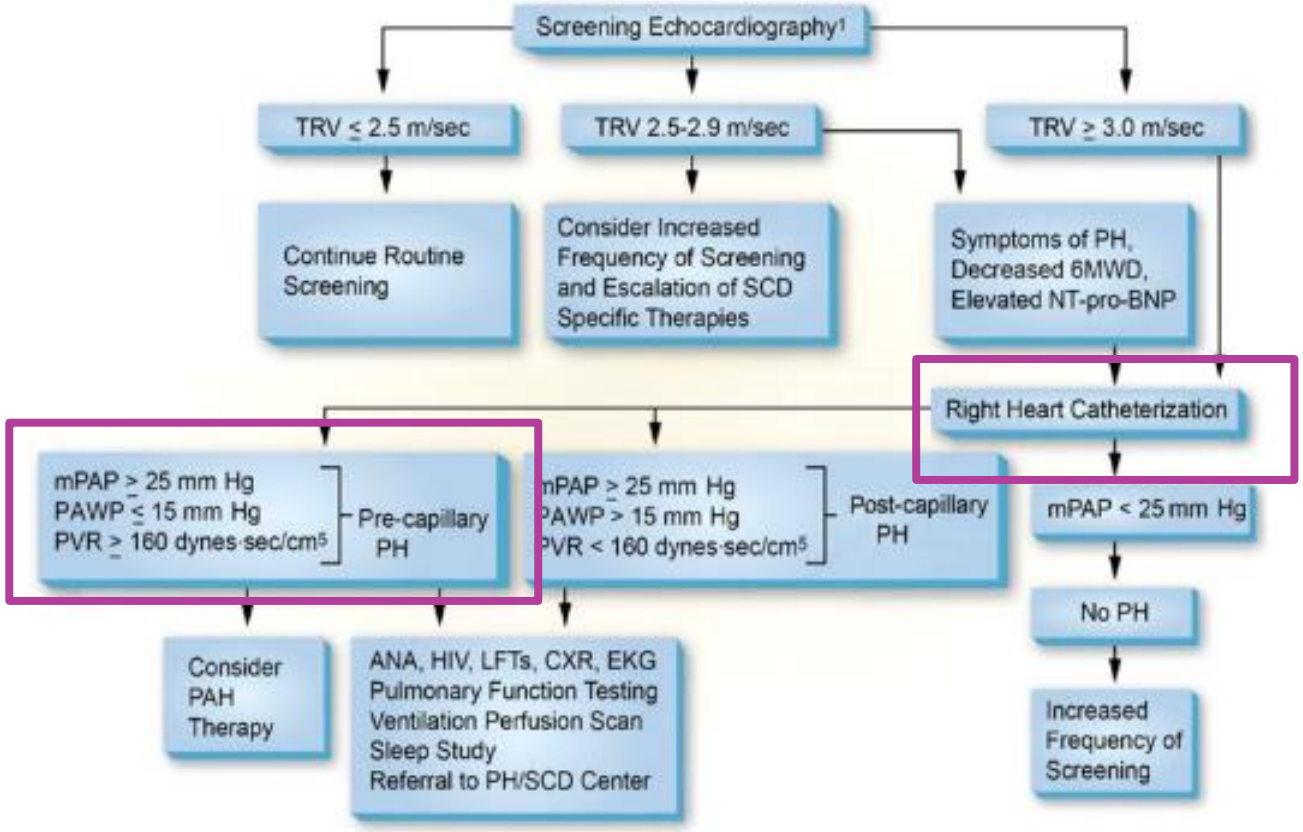

Klings et all, «An Official American Thoracic Society Clinical Practice Guideline: Diagnosis, Risk Stratification, and Management of Pulmonary Hypertension of Sickle Cell Disease», nov 2013.

PULMONARY HYPERTENSION

- ATS recommendations

4. For children with SCD who have evidence of PH by echocardiogram, the following are recommended:
   a. Children with SCD should undergo further cardiopulmonary evaluation, including pulmonary function testing, polysomnography, assessment of oxygenation, and evaluation for thromboembolic disease (*Class I; Level of Evidence C*).
   b. Children with SCD should undergo cardiac catheterization before the initiation of PAH-specific drug therapy (*Class I; Level of Evidence C*).
5. BNP and NT-proBNP measurements can be useful in screening for PH in patients with SCD (*Class IIa; Level of Evidence C*).

Adman et all, «Pediatric Pulmonary Hypertension Guideline from the American Heart Association and American Thoracic Society», Circulation, nov 2015.

PULMONARY HYPERTENSION

- Management
  - Multidisciplinary team!
  - O2 for Sat >= 90% rest/exertion
  - Treat OSA
  - Diuretics
  - Hydroxyurea and transfusions
  - Anticoagulation

PULMONARY HYPERTENSION

- ATS recommendations

6. With the diagnosis of PH in children with SCD, optimization of SCD-related therapies (eg, blood transfusions, hydroxyurea, iron chelation, and supplemental oxygen) is recommended (*Class I; Level of Evidence C*).
7. PAH-targeted therapy should not be used empirically in SCD-associated PH because of potential adverse effects (*Class III; Level of Evidence C*).
8. PAH-targeted therapy may be considered in patients with SCD in whom there is confirmation of PH with marked elevation of PVR without an elevated pulmonary capillary wedge pressure by cardiac catheterization (*Class IIb; Level of Evidence C*).

Adman et all, «Pediatric Pulmonary Hypertension Guideline from the American Heart Association and American Thoracic Society», Circulation, nov 2015

PULMONARY HYPERTENSION

- Screening
  - Studies do not demonstrate a better outcome with screening BUT
  - Symptoms often late in the course of disease
  - TRV > 2.5 m/sec
    - Associated with increased risk of death in adult
    - Associated with future reduced exercise capacity in children >= 8 years old
- Canadian consensus recommendation
  - Echocardiography every 5 years starting at 3 years old

Verhovsek et all, «Consensus Statement on the Care of Patients With Sickle Cell Disease in Canada», CanHeam Ottawa, 2015.

SLEEP DISORDERED BREATHING

- Increased incidence and severity
- Nighttime desaturations +/- OSA frequent
- OSA
  - Frequent comorbidity
  - Estimated prevalence 10-20%
  - Contributes to frequency of vaso-occlusive crisis and chronic cardiovascular disease

SLEEP DISORDERED BREATHING

- Prevalence in asymptomatic patients?
  - 1 screening study in 38 patients: 20 (53%) nocturnal desaturations ($SaO_2 < 92\% > 5\%$ of time)
- Etiology? Probably multifactorial
  - Reduced upper airway diameter
  - Increased adenoid and tonsillar size
  - Alteration of the O_2 dissociative curve
  - Decreased O_2 transport capacity due to anemia
  - Ventilation-perfusion anomalies

Needleman et all, «Mechanisms of nocturnal oxyhemoglobin desaturation in children and adolescents with sickle cell disease», Pediatr Pulmonol. 1999;28(6):418.

SLEEP DISORDERED BREATHING

- Look for symptoms!
- Usual indications PSG
  - Snoring, non-restorative sleep, gasping, choking, apneas, hypersomnolence, pulmonary hypertension
- Consider PSG
  - Unexplained hypoxemia, recurrent acute chest syndrome or vaso-occlusive crisis

SLEEP DISORDERED BREATHING

- Usual management
  - Including evaluation of adenotonsillar hypertrophy
- Hydroxyurea may decrease nocturnal hypoxia

VENOUS THROMBOEMBOLISM AND PULMONARY THROMBOSIS

- Hypercoagulable state
- D-dimers are increased at baseline and change with vaso-occlusive episodes
- Screening scores have bad predictive value
- Diagnosis by Angio-scan if clinical suspicion
  - Acute or progressive dyspnea
  - Lower extremity edema
  - Failure to respond to treatment of acute chest syndrome
  - Presence of other risk factors

PULMONARY FIBROSIS

- Recurrent acute chest syndromes with pulmonary infarction
- Clinical presentation
  - Dyspnea
  - Honeycombing
  - Restrictive pattern
  - Decreased DLCO
- No specific treatment
- Prevention of acute chest syndrome

PULMONARY FUNCTION TEST ABNORMALITIES - CHILDREN

- Evolution of PFT:

  normal -> obstructive -> restrictive
- Spirometry 5-18 years old
  - 71% normal
  - 16% obstructive pattern
  - 13% restrictive pattern
- Most frequent abnormality during adolescence
  - Restrictive pattern
    - 0.9% of 8-year-old children
    - 18.7 % of 17-year-old adolescents

Wilmott et all «Kendig and Chernick's Disorders of the Respiratory Tract in Children» 8e édition, 2012, p. 1019-1025.

PULMONARY FUNCTION TEST ABNORMALITIES - CHILDREN

- PFT are recommended annually from 6 years old
- Plethysmography is recommended starting from 6 years old
  - Every 5 years if no asthma or acute chest syndrome
  - Every 2-3 years if asthma or acute chest syndrome

Wilmott et all «Kendig and Chernick's Disorders of the Respiratory Tract in Children» 8e édition, 2012, p. 1019-1025.

CONCLUSION

- Sickle cell disease
  - Frequent AR hemoglobinopathy with multiple respiratory complications
- Acute chest syndrome
  - New infiltrate on chest X ray + respiratory symptoms or fever
  - Rapid management
- Pulmonary hypertension
  - Echocardiographic screening every 5 years
  - Diagnosis by cardiac catheterization

CONCLUSION

- Obstructive sleep apnea is frequent
  - Look for it on history
  - Consider PSG if symptoms, unexplained hypoxemia, recurrent acute chest or vaso-occlusive episodes or enuresis
- Asthma is also frequent
  - Look for it since it ↑ acute chest and vaso-occlusive episodes
- PFT often abnormal
  - Recommended every year
- Saturation often decreased
  - Measure it at every visit

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THANK YOU!