SICKLE CELL DISEASE

SICKLING AND UN-SICKLING CYCLE
This multi-step and multi-cellular process leads to short-term tissue hypoxia, long-term inflammation, and endothelial vasculopathy.

(CHRONIC INFAMMATORY DISEASE)
**SICKLE CELL VASCULOPATHY**

- Proliferative changes in Intima and Smooth muscle.
Acute and chronic vasculopathy and persistent anemia > HYPOXIA

Progressive & persistent CHRONIC ORGAN DAMAGE

Irrespective of severity of the disease

Starts in early the infancy- 6 months

Overt clinical symptoms come late
CHRONIC ORGAN DAMAGE

Acute pain
Severe anemia
Increased infections
Hospitalization

Renal damage
PULMONARY COMP.

Lt. ventricle diastolic dysfunction
Osteopathy
Retinopathy

Cerebro-vascular & parenchymal damage

Neuro-cognitive deg.
Poor scholastic performance
Poor growth
Chronic pain

Functional asplenia
Auto-splenectomy

“DOING WELL”

POOR QUALITY OF LIFE
MORBIDITY ++
Premature DEATH
INCREASED HEALTH EXPENDITURE

Most severely affected sickle children born in low-income countries still die un-diagnosed, usually from:

- Bacteremia, Meningitis
- Acute chest syndrome
- Splenic sequestration etc.
- Malaria

NATURAL ELIMINATION
Developed countries that provide NEONATAL DIAGNOSIS, COMPREHENSIVE CARE & HYDROXY UREA, most survive well into adult life.

- GENETIC COUNSELING
- PRENATAL DIAGNOSIS

is reducing the birth of sickle patient.
SICKLE IN INDIA

Sickle Cell Disorders in India

Sickle belt
- Gujarat
- North Maharashtra
- Vidarbha
- Madhya Pradesh
- Chhattisgarh
- Telangana
- Andhra Pradesh
- Orissa

Kerala
Tamil Nadu
Karnataka
We are here

• PRENATAL DIAGNOSIS
• MARRIAGE COUNSELLING
PULMONARY COMPLICATIONS OF SICKLE CELL DISEASE

- Pathophysiology
- Comprehensive care
- Use of Hydroxy urea
- Infection control
- Early and effective t/t of the sickle crises

FATAL Pediatric Disease

CHANGING SCENARIO

Adult Chronic Organ Disease
According to the Cooperative Study of Sickle Cell Disease (CSSCD), a prospective multicenter study of 3,764 patients,

- > 20% of adults had pulmonary complications of SCD
- > 25% of death due to Acute Chest Syndrome and Pulmonary Hypertension

- Under-appreciated by healthcare providers.
# Pulmonary Complications of Sickle Cell Disease

## Acute
- Acute Chest Syndrome
- Asthma-like wheezing
- Venous or Arterial Thrombo-Embolism

## Chronic
- Pulmonary hypertension
- Asthma & like wheezing
- Venous Thrombo-Embolism
- Sleep Disordered Breathing
- Pulmonary fibrosis
ACUTE CHEST SYNDROME

• Most common cause of death
• Second most common cause of hospitalization

ACUTE CHEST SYNDROME is defined as a new radiographic finding of the lungs associated with fever, thoracic pain, respiratory symptoms & signs.
PATHOPHYSIOLOGY OF ACUTE CHEST SYNDROME

Ventilation-Perfusion Mismatch
## TREATMENT OF ACUTE CHEST SYNDROME

### SUPPORTIVE CARE
- Incentive spirometry
- Corticosteroids
- Bronchodilators
- Bronchoscopy - atelctasis
- Inhaled Nitric Oxide(NO)
- L-arginine (NO precursor)
- Anticoagulation,
- Encourage Early Ambulation

### Oxygenation - hypoxemia
- Non-invasive
- Invasive (mechanical)

### Aggressive Pain management

### Maintain Hydration

### Blood transfusion -
- Oxygen carrying capacity
- Reduce the % of HbS

### Antibiotics - Amoxy-clav, Ceftriaxone, Macrolide
PULMONARY HYPERTENSION IN SCD

- Starts in the childhood and adolescents. (3yr)
- SCD – Commonest cause of Secondary Pulmonary Hypertension
NIH STUDY at HOWARD VALIDATED TRICUSPID VALVE REGURGITANT VELOCITY (TRV) FOR DETECTING PH IN SCD

<table>
<thead>
<tr>
<th>Tricuspid Regurgitant Velocity</th>
<th>Prevalence Among SCD Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt; 2.5 m/sec</td>
</tr>
<tr>
<td>Mild</td>
<td>2.5-2.9 m/sec</td>
</tr>
<tr>
<td>Severe</td>
<td>&gt; 2.9 m/sec</td>
</tr>
</tbody>
</table>
AMERICAN THORACIC SOCIETY (ATS) GUIDELINES FOR M/M OF PULMONARY HYPERTENSION 2014

ATS CLINICAL PRACTICE GUIDELINE: SUMMARY FOR CLINICIANS
Series Editors: Carey Thomson and Kevin Wilson

Pulmonary Hypertension in Sickle Cell Disease
Margaret M. Hayes1, Amr Vedenurthy2, Gautam George2, Raed Daab2, Elizabeth S. Kling2, Roberto F. Machado3, Mark T. Gladwin2, Kevin C. Wilson4, and Carey C. Thomson2; for the American Thoracic Society Implementation Task Force

1Johns Hopkins University School of Medicine, Baltimore, Maryland; 2Mt. Auburn Hospital, Harvard Medical School, Boston, Massachusetts; 3Cleveland Clinic, Cleveland, Ohio; 4Boston University School of Medicine, Boston, Massachusetts; 5University of Illinois College of Medicine, Chicago, Illinois; and 6University of Pittsburgh Graduate School of Medicine, Pittsburgh, Pennsylvania

TRV: Tricuspid Regurgitant Jet Velocity
6MWD: 6-minute Walk Distance
NT-pro-BNP: N-terminal Pro-brain Natriuretic Peptide
mPAP: Mean Pulmonary Artery Pressure
PAWP: Pulmonary Artery Wedge Pressure
PVR: Pulmonary Vascular Resistance
MANAGEMENT OF PULMONARY HYPERTENSION

- Reduce the severity of hemolytic anemia
  - Hydroxyurea
  - Chronic blood transfusion
- Chronic Oxygen therapy for Hypoxic children
- Incentive spirometry
- Targeted therapy of PAH
- L-Arginine/ inhaled NO
- Chronic Anti-Coagulant therapy

Prevention
- Comprehensive care
  - EARLY SCREENING
    - Pulmonary function - 6 yrs
    - Echo screening - 8 yrs.
  - EARLY DIAGNOSIS WILL GIVE US AN OPPORTUNITY PREVENT FURTHER DAMAGE
Chronic Pulmonary Complications of Sickle Cell Disease
Alem Mehari, Klings, BOSTON CHEST 2016 –

Up to 70 percent of children with SCD have airway hyper-responsiveness

Asthma is associated with acute chest syndrome and pain in children with sickle cell anemia
Michael R. DeBaun, MD
ACS is more common in Asthmatics

Asthma in children with sickle cell disease and its association with acute chest syndrome
Knight-Madden JM, THORAX. 2005;60(3):206.
Effective Asthma therapy reduces the pulmonary complication of SCD.

Asthma should be treated according to Standard guidelines for the non- sickle children.
OBSTRUCTIVE SLEEP APNEA

- OSA is also an inflammatory disease.
- Both OSA and SCD aggravate each other.
- As many as 79 percent of children and 44 percent of adults with SCD had SDB.
- Correction of obstructive sleep apnea decreases V O crises, ACS, and cerebrovascular disease.
VENOUS-THROMBO-EMBOLISM SCD

Under-recognized but prevalent in SCD.

SCD is a chronic inflammatory disease associated with
  hypercoagulable state
  Endothelial dysfunction with
  Abnormalities in coagulation and platelet function

Pulmonary artery thrombosis was found in autopsies.

The optimal treatment not known,
we follow the usual guidelines for VTE treatment.
- Recurrent episodes of acute chest syndrome (ACS) with pulmonary infarction.
- Progressive dyspnea
- A restrictive pattern on pulmonary function tests
- Scattered areas of honeycombing - CT
- No specific therapy for pulmonary fibrosis
COMPREHENSIVE CARE IN SCD

- Neonatal screening test ~ below 2 months in susceptible communities (HPLC)
- Penicillin prophylaxis >2 months of age, Malarial prophylaxis in endemic regions
- Immunization – IAP recommendation for Immunocompromised
- Timely and appropriate treatment of acute illnesses and crises
- Hydroxy urea
- Chronic blood transfusion, chelation.
HYDROXY UREA

- A Myelosuppressive agent,
- Only effective drug (Wonder drug, Ideal drug)
- May alter natural history of sickle cell disease.
- May reverse the Organ Damage.
• Increases Intracellular Fetal Hemoglobin
• Homogeneous Distribution Of Fhb
• Neutrophil Count
• Retic Count
• Platelet Count
• Increases ‘nitric-oxide’ Production

Potent Local Vasodilatation And Improved Vascular Response

PREVENTS SICKLE VASCULOPATHY
Hydroxyurea is safe and well tolerated. Oral, inexpensive, once daily dosing.

- Works in all ages
- No Drug resistance.
- No clinical adverse events identified,
- Hydroxyurea treated pt’s survive longer than those not treated with the drug.
Acute pain
Severe anemia
Increased infections
hospitalization

Poor growth
Chronic pain
Splenic dysfunction

Splenomegaly,
Asplenia,
Splenic infacts
Splenic sequestration
crisis
Hypersplenism.

POOR GROWTH

DELAYED
PUBERTY

Endocrine
dysfunction
Renal damage
Pulmonary-hypertension
Lt. ventricle
diastolic
dysfunction
Osteopathy
Retinopathy

Neuro-cognitive deg.

Poor scholastic performance

Cerebro–vascular &
parenchymal damage

ALL SICKLE
AFFECTED
Pts.
From 6 months
of age.

to enjoy healthy and productive lives with good quality
MONITORING & DOSE

- WBC count between 5000 - 8000.
- MCV should be +- 100 – Fetal Hb
- Platelet count > 80,000

Start with 20 mg/ kg to reach to MTD (Maximum Tolerable Dose) – 35 mg/ kg/ day

Monitor Liver & Renal functions Initially for few months
ADVERSE EFFECTS

REVERSIBLE Transient Bone marrow suppression:
WBC <2000/ , Platelet count < 80,000/

The risk of HU therapy is acceptable compare to with the risk of untreated Pts.

Contraception is MUST.
BLOOD TRANSFUSION IN SCD

Top-up transfusion- if Hb is very less.
Hb ~10 gm. Partial or Total - Exchange

- Reduce Sickle Hb (30%) and increase HbA
  Prevent further Voso-occlusive crises and
  Increase the oxygen carrying capacity of blood.

Chronic blood transfusion
For prevention of recurrent ACS, Pulmonary Hypertension & cerebral strokes

- keep the sickle Hb below 30%. (HU is not effective)
- To Suppress Erythropoiesis.

Short term < 6 months,
Long term >2 yrs. (Chelation)
BONE MARROW TRANSPLANTATION

The only available CURATIVE OPTION in individuals with SCD.

GENE THERAPY + STEM CELL TRANSPLANTATION
HUMAN TRIAL IN VOLUNTEERS IN DANA-FERBUR , BOSTON

ENDARI
Mechanism of action: L-glutamine serves as an antioxidant in sickle red blood cells (RBCs) to elevate the NAD redox potential, thereby countering the oxidant dependent pathophysiology of sickle RBCs, such as sickle RBC adhesion to endothelium and the resulting vascular occlusion.

Voxelotor improve oxygen delivery which makes it a potential disease modifying therapy in SCD
CONCLUSION

- Lung is the most important organ in SCD.
- Sickle is a Chronic Inflammatory disease
- Keep the lungs healthy.
- HYDROXY UREA is safe and effective in infants and children, It can prevent sickle vasculopathy.
THANKS

SICKLE IS NOT SIMPLE

THANKS