Sickle Cell Anemia

Case

- A 15-year-old African-American female presents to the emergency room with complaints of bilateral thigh and hip pain. The pain has been present for 1 day and is steadily increasing in severity. Acetaminophen and ibuprofen have not relieved her symptoms. She denies any recent trauma or excessive exercise.

- She does report feeling fatigued and has been having burning with urination along with urinating frequently. She reports having similar pain episodes in the past, sometimes requiring hospitalization.

- On examination, she is afebrile (without fever) and in no acute distress. No one in her family has similar episodes.
- Her conjunctiva and mucosal membranes are slightly pale in coloration.
- She has nonspecific bilateral anterior thigh pain with no abnormalities appreciated. The remainder of her examination is completely normal.
- Her white blood cell count is elevated at 17,000/mm3, and her hemoglobin (Hb) level is decreased at 7.1 g/dL. The urinalysis demonstrated an abnormal number of numerous bacteria.

Learning objectives

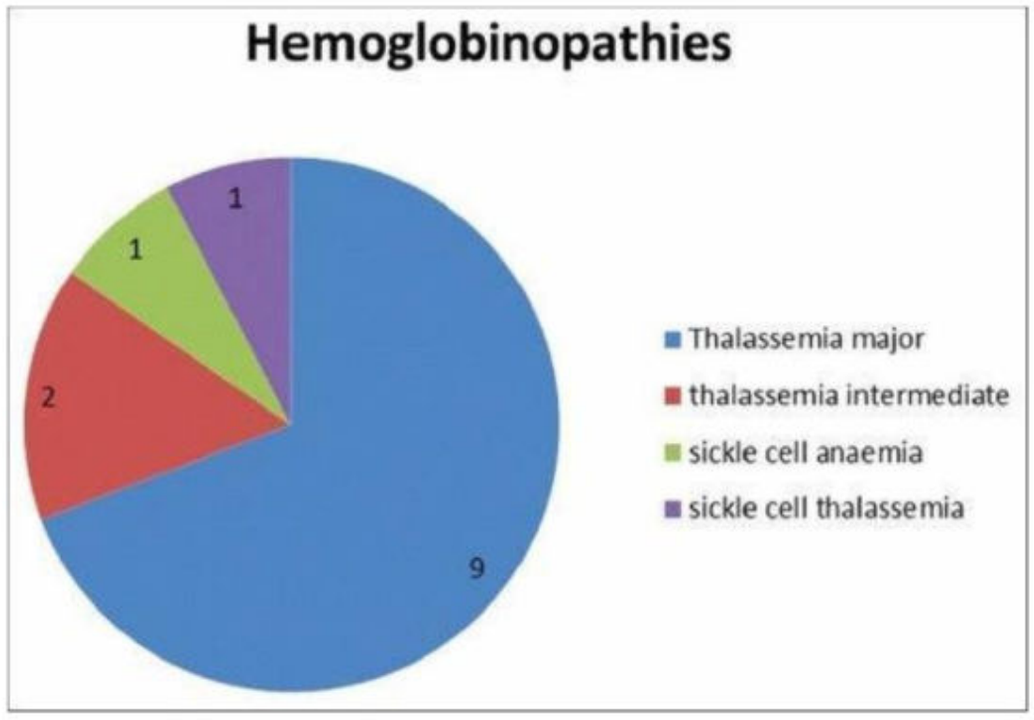
- **What is the most likely diagnosis?**
- **What is the molecular genetics behind this disorder?**
- **What is the pathophysiologic mechanism of her symptoms?**

Hemoglobinopathies

1. Group of genetic disorders caused by production of a structurally abnormal hemoglobin molecule(**Qualitative**);

2. Synthesis of insufficient quantities of normal haemoglobin(**Quantitative**);

- or, rarely, both.

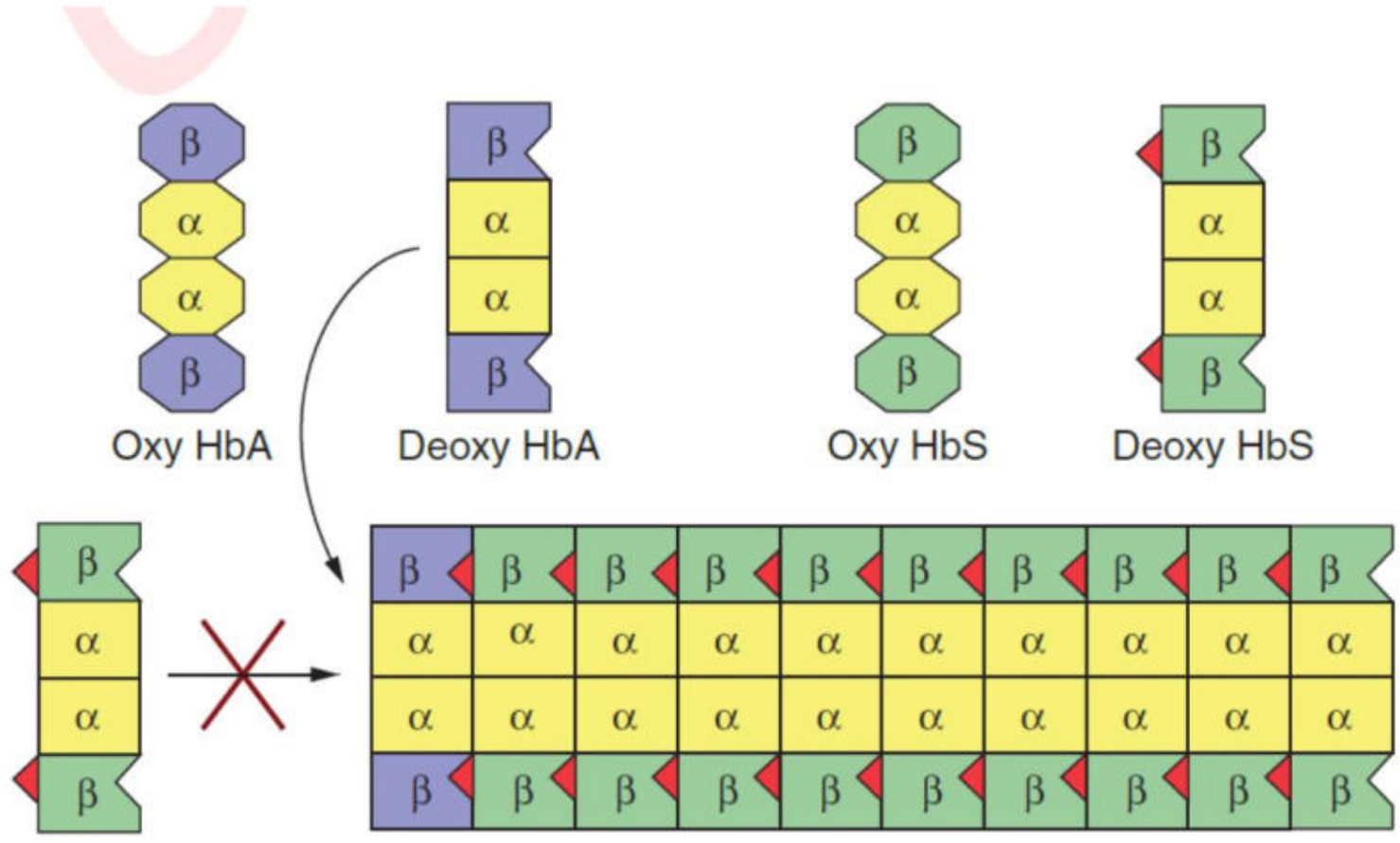


Diagnosis of Case: Sickle cell Anemia

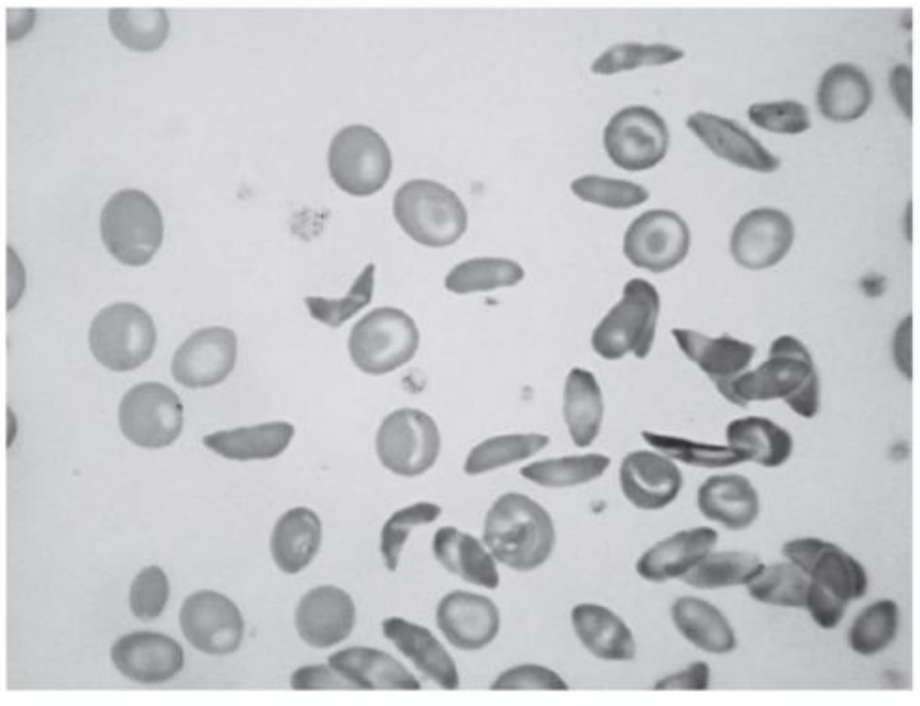
Molecular Mechanism

- **Autosomal Recessive**
- **GTG →GAG** at 6th position of **β** globin chain.
- The replacement of the **charged glutamate with the nonpolar valine** on surface of β globin chain
- The intrinsic oxygen binding properties of HbA and HbS are the same, however, the **solubility of deoxy HbS is reduced** because of exposure of **Val-6** at the **surface of the β -chain.**
- Since hemoglobin is present at very high concentrations in the red blood cell, **deoxy HbS will precipitate inside the cell.**
- The precipitate takes the form of **elongated fibers** because of the association of complementary hydrophobic surfaces on the β- chains of deoxy HbS.
- At oxygen saturations found in arterial blood, the oxy HbS predominates and HbS does not precipitate because Val-6 of the β-chain is not exposed to the surface

Hydrophobic Sticky Patch of deoxy HbS

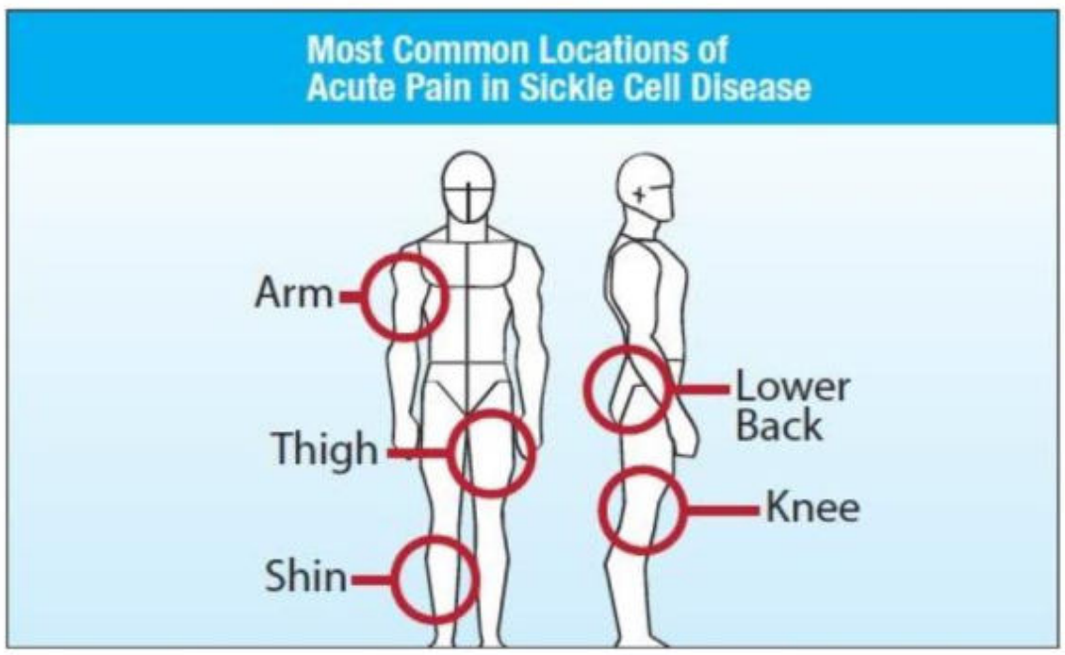


- At low oxygen tension, deoxyhemoglobin S polymerizes inside the RBC, forming a network of insoluble fibrous polymers that stiffen and distort the cell, producing rigid, misshapen RBC. Such sickled cells frequently block the flow of blood in the narrow capillaries

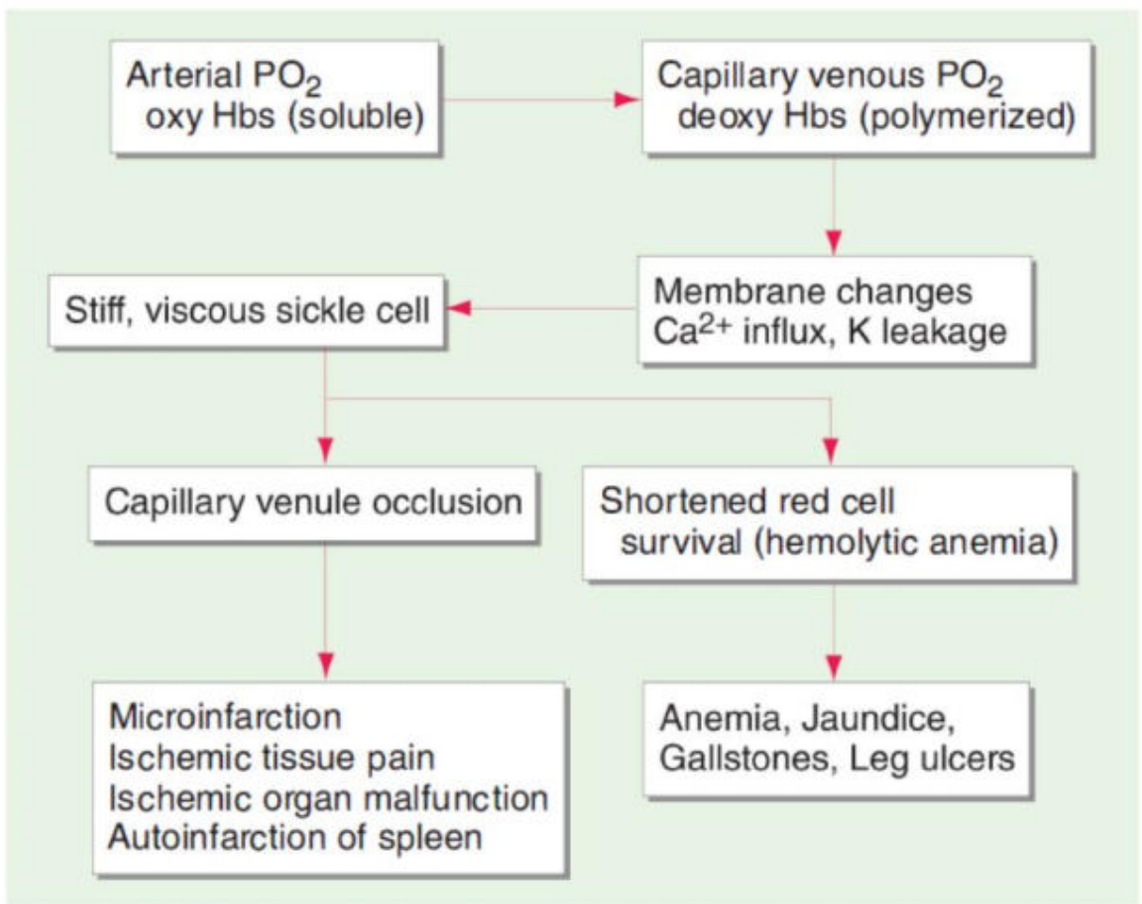


Pathophysiologic Mechanism of Symptoms

- This interruption in the supply of oxygen leads to localized anoxia (oxygen deprivation) in the tissue, causing pain and eventually death (infarction) of cells in the vicinity of the blockage.
- Sickle cell crisis



Pathophysiology of Sickle cell Crisis



Symptoms of SCD

- **Vaso-occlusive events** result in tissue ischemia leading to acute and chronic pain as well as organ damage that can affect any organ system, including the bones, spleen, liver, brain, lungs, kidneys, and joints.
- **Dactylitis** (pain and/or swelling of the hands or feet) is often the earliest manifestation of SCD.
- In children, the spleen can become engorged with blood cells in a "**Splenic sequestration**.".

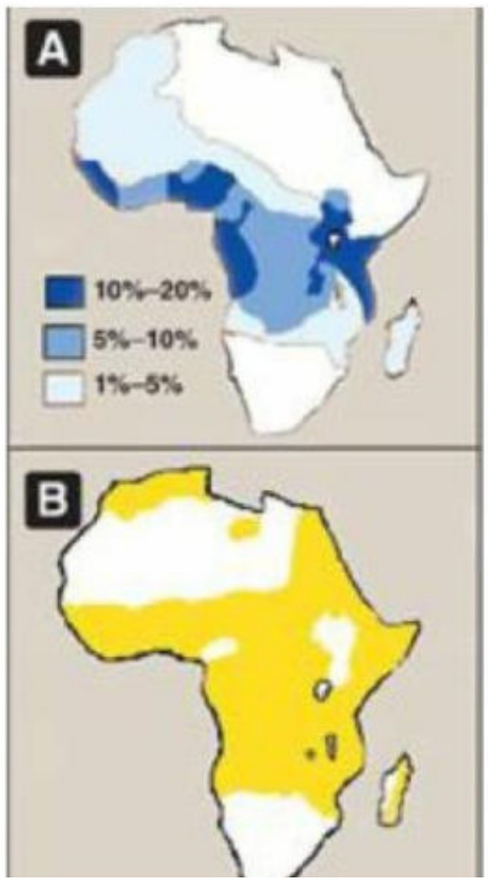
Symptoms of SCD

- The spleen is particularly vulnerable to infarction and the majority of individuals with SCD who are not on hydroxyurea or transfusion therapy become functionally **asplenic** in early childhood, increasing their risk for certain types of bacterial infections.
- **Acute chest syndrome** is a major cause of mortality in SCD.
- **Chronic hemolysis** can result in varying degrees of anemia, jaundice, cholelithiasis, and delayed growth and sexual maturation.

Bender MA[1]. **Sickle Cell Disease.** GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. 2003 Sep 15 [updated 2017 Aug 17].

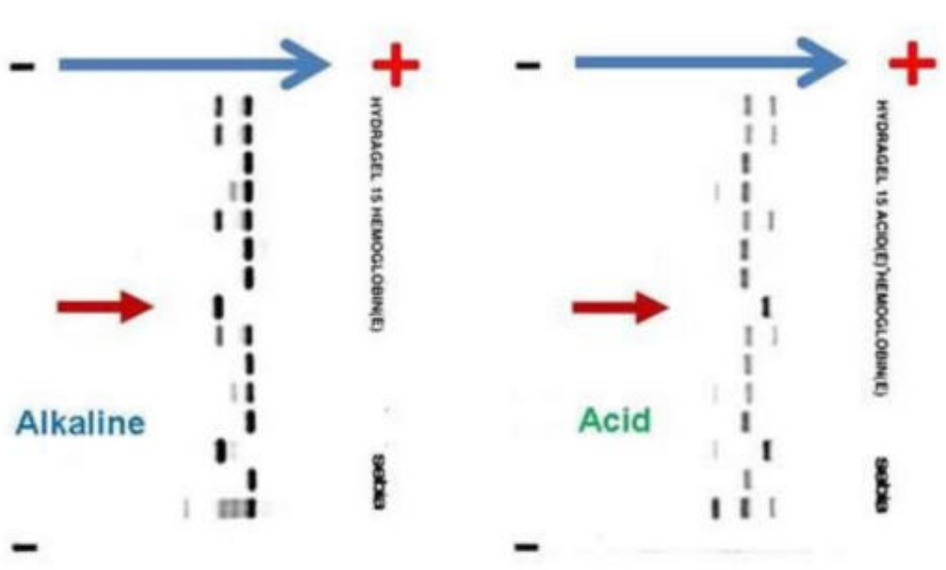
Possible selective advantage of the heterozygous state

- high frequency of the bS mutation among black Africans



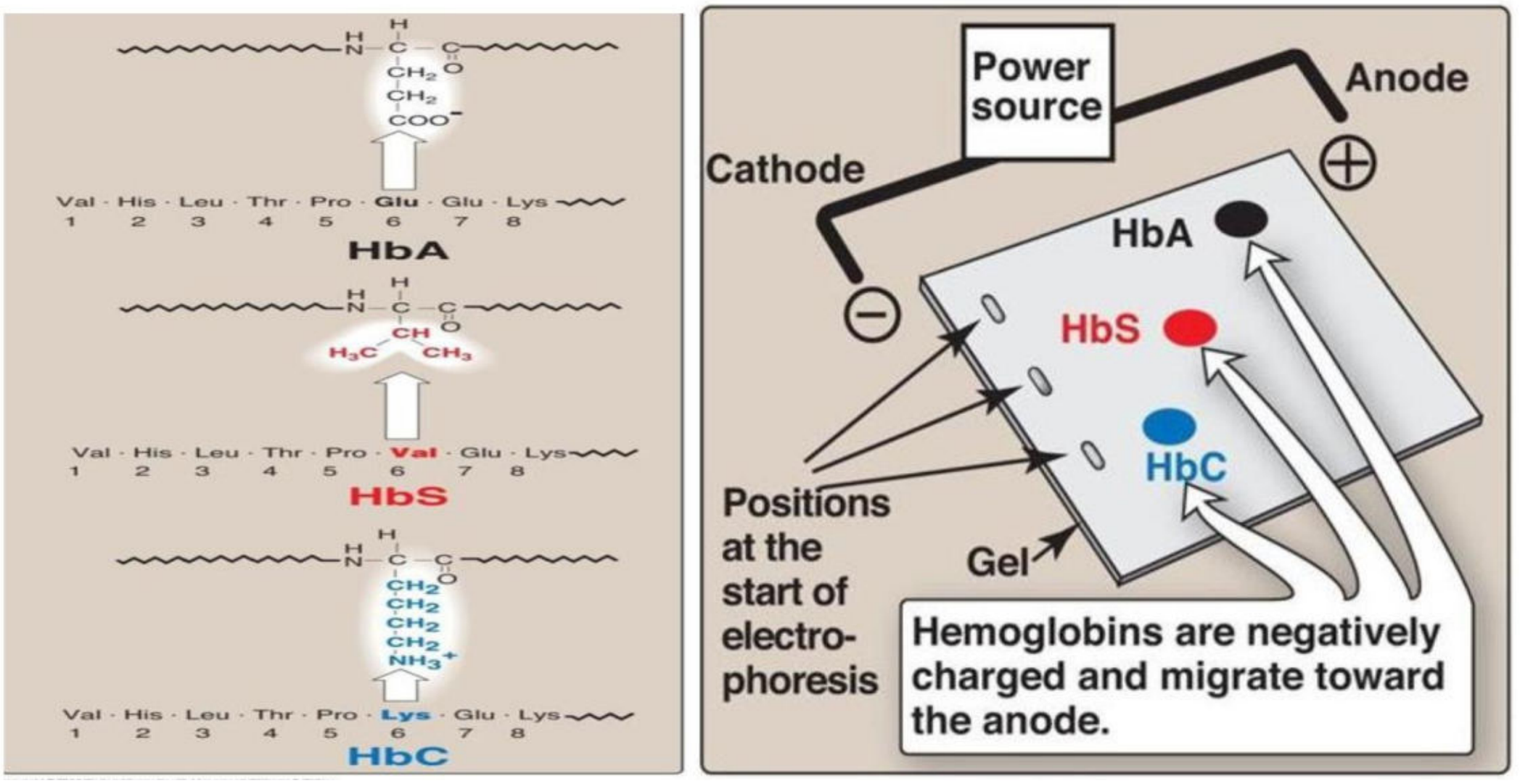
Diagnosis

- **Hemoglobin Electrophoresis**
- **Full blood count**
- **Peripheral blood smear.**



http://www.hematology.org/Fellows/Case-Studies/725.aspx

Hb Electrophoresis



Treatment

- **Management of pain** episodes includes hydration, anti-inflammatory agents, and pain medication
- **Fever** and suspected infection is treated with appropriate antibiotics
- Life-threatening or severe complications (e.g., severe acute chest syndrome, aplastic crisis, and stroke) are often treated with red **blood cell transfusion**
- **Splenectomy** may be necessary for splenic sequestration
- **Hydroxyurea** can decrease the frequency and severity of vaso-occlusive processes, reduce transfusion needs, and increase life span.

Treatment

- **Hydroxyurea(FDA Approved):**

By inhibiting the enzyme ribonucleotide reductase, hydroxyurea has been shown to increase the levels of fetal Hb (HbF, α2γ2) by mechanisms not fully understood.

Increase in HbF concentrations has the effect of decreasing HbS levels and its polymerisation in the red blood cell.

- **Glutamine** has received FDA approval for the prevention of acute complications in individuals with SCD age five years and older(antioxidant).
- **Stem cell transplantation** may be an option in selected individuals

Summary and Discussion of the Case

- This 15-year-old female's description of her pain is typical of a sickle cell pain crisis.
- Many times, infection is a trigger, most commonly pneumonia or a urinary tract infection. This case is consistent with a urinary tract infection, indicated by her symptoms of urinary frequency, and burning with urination (dysuria). Her white blood cell count is elevated in response to the infection.
- The low hemoglobin level is consistent with sickle cell anemia

Summary

- Since she is homozygous (both genes coding for sickle hemoglobin), both her parents have sickle cell trait (heterozygous) and thus do not have symptoms.
- The diagnosis can be established with hemoglobin electrophoresis.
- The tendency for deoxy HbS to precipitate is why clinical manifestations of sickle cell anemia are brought on by **exertion** and why **treatment includes administration of oxygen.**

Thank You!