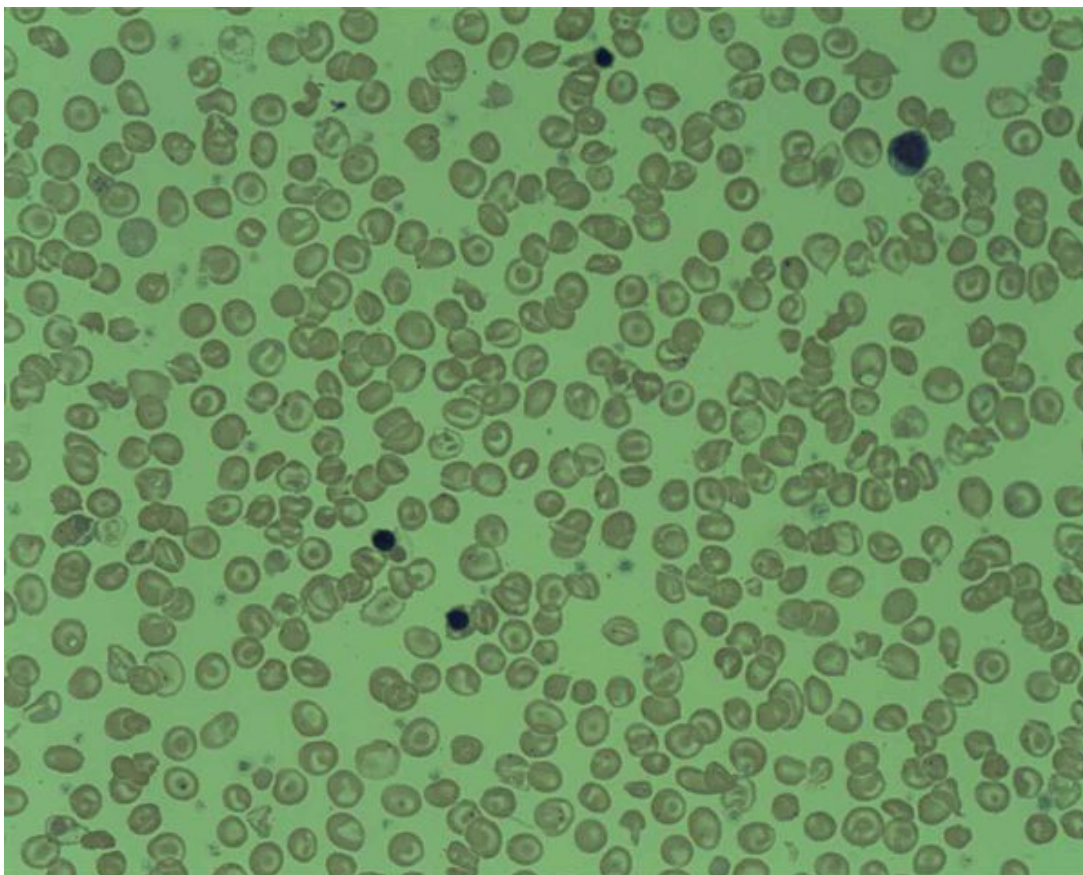


## Thalassemia in Children — Symptoms and Treatment

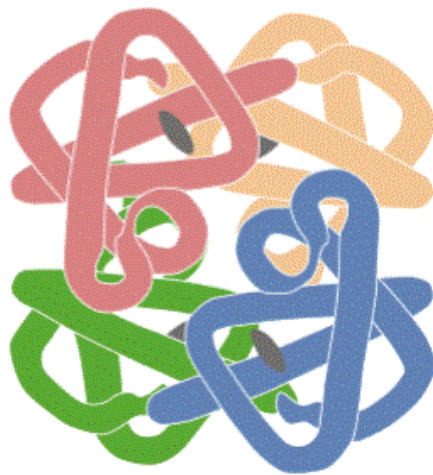
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**Thalassemias are a group of inherited disorders that are characterized by decreased production of the alpha or beta globin chains. The amount of the produced normal hemoglobin within the red blood cells correlates with the severity of the symptoms. Fetuses with alpha-thalassemia major usually die. Children with beta-thalassemia major are usually dependent on repeated blood transfusions. Splenectomy is the only therapeutic option that is known to result in improvement of symptoms and severity of the anemia in children with major thalassemia. Bone marrow transplantation is becoming a possible curative option for selected patients with beta-thalassemia major.**



### Overview

Thalassemias can be defined as a group of disorders that are **inherited and involve abnormal hemoglobin synthesis**. Thalassemias can be classified according to the involved hemoglobin gene and the severity of the condition.



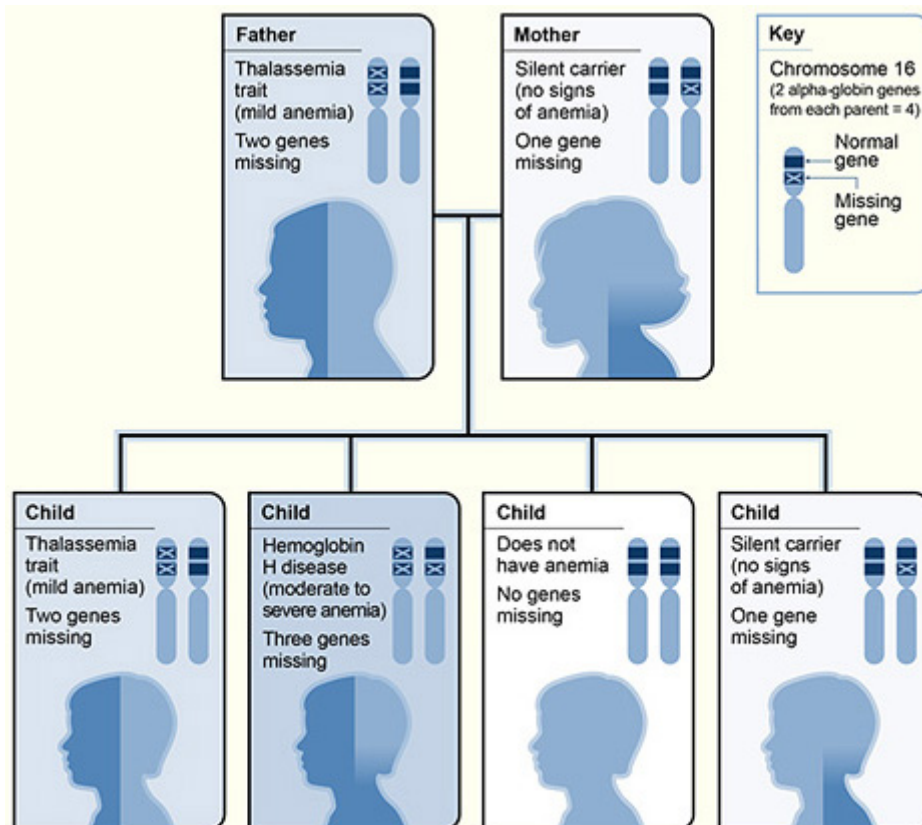
subunits  $\alpha$  -  $\beta$

"Thalassemia" Image created by Lecturio

In the genome:

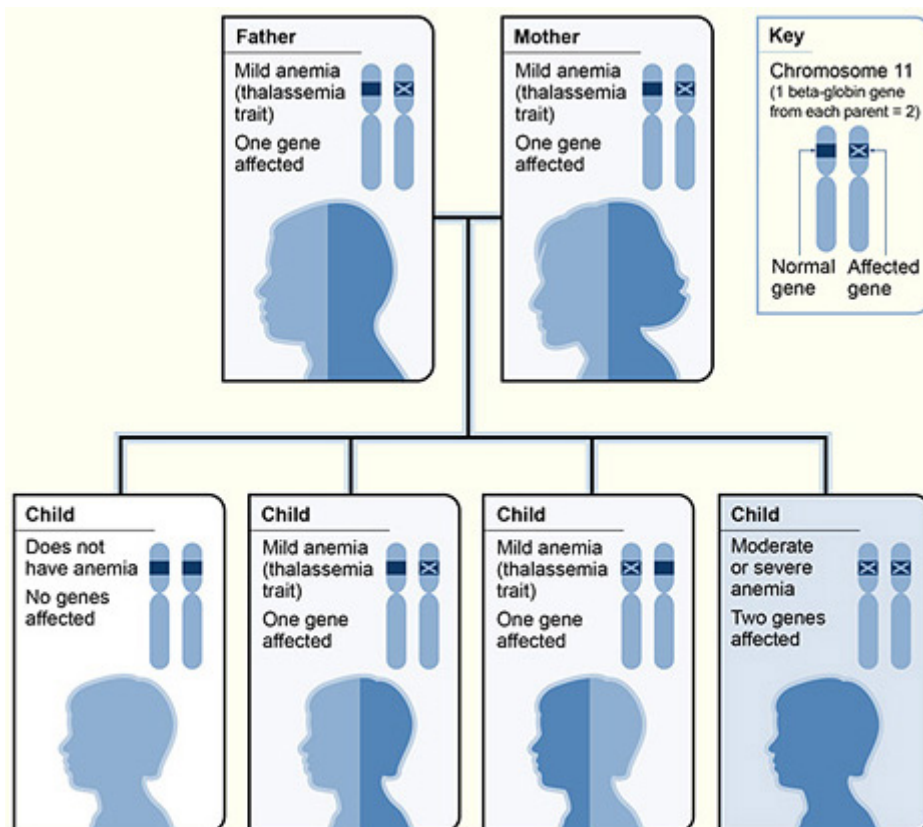
- 2 copies of  $\beta$  gene (chromosome 11)
- 4 copies of  $\alpha$  gene (chromosome 16)

**Alpha-thalassemias** include silent carrier alpha-thalassemia, alpha-thalassemia trait, Hb H disease and alpha-thalassemia major. Silent carrier alpha-thalassemia usually has normal hemoglobin (Hb) on electrophoresis. Patients with alpha-thalassemia trait have a mild anemia and a reduced red blood cell count and size. Patients with Hb H disease have mild to moderate anemia, splenomegaly and grossly abnormal red blood cell indices. Those with alpha thalassemia major have the most severe form of thalassemia, involving the alpha chain of the hemoglobin molecule.



The picture shows one example of how alpha thalassemia is inherited. The alpha globin genes are located on chromosome 16. A child inherits four alpha globin genes (two from each parent). In this example, the father is missing two alpha globin genes and the mother is missing one alpha globin gene. Each child has a 25% chance of inheriting two missing genes and two normal genes (thalassemia trait), three missing genes and one normal gene (hemoglobin H disease), four normal genes (no anemia), or one missing gene and three normal genes (silent carrier).

**Beta-thalassemias** can also be classified into silent carrier beta-thalassemia, beta-thalassemia trait, beta-thalassemia intermedia and beta-thalassemia major. Patients with beta-thalassemia major are transfusion dependent.



The picture shows one example of how beta thalassemia is inherited. The beta globin gene is located on chromosome 11. A child inherits two beta globin genes (one from each parent). In this example, each parent has one altered beta-globin gene. Each child has a 25% chance of inheriting two normal genes (no anemia), a 50% chance of inheriting one altered gene and one normal gene (beta thalassemia trait), or a 25% chance of inheriting two altered genes (beta thalassemia major).

**Staging of thalassemia is based on the number of packed red blood cells** the patient has received. Patients who received less than 100 units are considered as stage I. Those who have received between 100 and 400 units of packed red blood cells are considered as stage II patients. Patients with symptoms and signs suggestive of heart failure, usually have received more than 400 units of packed red blood cells, are considered as stage III patients.

## Epidemiology of Thalassemia in Children

Beta and alpha-thalassemia major are **very rarely seen, but their incidence is rising**. Approximately, 10 to 14 new cases of beta-thalassemia major are diagnosed per year in California alone. The most likely cause of higher numbers of thalassemia cases in California can be explained by the larger number of Asian immigrants in that state. Beta thalassemias are more commonly diagnosed in people from an Asian heritage, especially Southeast Asia.

Beta thalassemias are also more commonly recognized in Mediterranean countries such as Greece, Italy and Spain. Beta thalassemias are also commonly diagnosed in the Middle East, Africa and Eastern Europe.

**Mortality rates of thalassemias are dependent on the exact type of disease.**

Alpha thalassemia major is usually fatal. Patients with beta-thalassemia major also have a very high mortality rate. On the other hand, patients with Hb H disease usually survive long if proper treatment and close follow-ups are provided.

The most common cause of death in children with beta-thalassemia major is heart failure. Heart failure can happen as a consequence to iron overload, or because of the severe anemia. Patients can also develop liver disease, which carries a significantly increased risk of morbidity and mortality.

The thalassemias usually have an equal incidence in both sexes without any significant differences. Beta thalassemia major can be diagnosed at birth or shortly after once the levels of Hb F drops. Neonates with unexplained hypochromic microcytic anemia should be evaluated for possible thalassemia.

## Pathophysiology of Thalassemia

Hereditary mutations in the alpha or beta globin chain genes are responsible for the decreased production of the affected globin chain. The decreased production of the affected globin chain is usually associated with an **imbalance in the production of the other globin chains is usually intact**. The accumulation of the other intact globin chains is responsible for the induction of cellular apoptosis. The alpha-chain genes are located on chromosome 16, while the beta-globin genes are located on chromosome 11.

The degree of decreased production of a certain globin chain can range from slightly decreased production to absolute absence. Patients with an absolute absence of a certain globin chain, usually the beta globin chain, usually have a more severe form of the disease.

When the production of certain globin chains is decreased, the total amount of functional hemoglobin within the red blood cell is also decreased. **Because of the decreased hemoglobin content within the red blood cells, the cells usually appear hypochromic and their size is reduced.**

More than 200 mutations have been described to affect the beta globin chain genes. These mutations can be **major deletions, single base changes, small deletions or insertions of one or two bases at critical sites within the genes**. The end result of these different mutations has decreased the production of the beta globin chain. An example of the mutations within the beta genes includes a single base change in an exon that generates a stop codon in the coding region of the mRNA. Because of this nonsense mutation, premature termination of the beta-globin chain synthesis happens and nonviable beta chains are formed which are toxic to the cell and its membrane and causes red blood cell destruction.

Additionally, the beta-globin chains in humans have two introns and precise splicing of the produced mRNA is essential for the production of viable beta chains. Mutations within the consensus sequence can result in improper splicing. Inefficient slicing of the encoded mRNA is associated with decreased and impaired beta globin synthesis, and the production of some common abnormal hemoglobins such as Malay, E, and Knossos.

Mutations within the promoter region of the beta-globin gene are associated with decreased beta-globin gene transcription and, ultimately, decreased beta-globin production.

Patients with beta-thalassemia major usually have **elevated levels of HbA2 which is produced from the coupling between alpha-chains and  $\delta$ -globin chains**. When mutations in the  $\delta$ -globin chain gene co-exist with mutations in the beta-globin chain gene, the levels of HbA2 are usually normal or HbA2 can be absent.

Humans have four copies of the alpha-globin gene, two alpha genes on each chromosome 16. The deletion of one copy is responsible for silent carrier alpha-thalassemia. The **deletion of two copies from the same chromosome or one copy of each chromosome is responsible for alpha thalassemia trait**. Hb H disease is characterized by the deletion of three alpha-globin genes, while the deletion of the four genes is usually associated with the fatal form of the disease known as alpha thalassemia major.

Patients who are **silent carriers of beta-thalassemia usually have a very mild mutation** that results in slightly impaired with beta-globin production without any major symptoms. Beta-thalassemia trait is characterized by elevated levels of HbA2, or fetal hemoglobin, due to the substantially decreased production of viable beta-globin chains.

## Clinical Presentation of Thalassemia in Children



**Image:** "Frontal bossing and prominent maxilla (thalassemic facies) in a child suffering from thalassemia major." by Taneja R, Malik P, Sharma M, Agarwal MC License: [CC BY 2.0](https://creativecommons.org/licenses/by/2.0/)

Children with beta-thalassemia major usually have more specific and profound symptoms of severe anemia and splenomegaly. Patients might have a fever and, usually, fail to thrive. Beta-thalassemia major is usually fatal within five years of the child if it is not treated.

Patients with milder forms of beta or alpha thalassemia usually present with pallor, splenomegaly and an abnormal complete blood count with the hypochromic microcytic anemia. Bony abnormalities like frontal bossing, prominent jaw bones, and dental malocclusion due to defective erythropoiesis. Endocrinopathies like diabetes, thyroid dysfunction are seen due to hypermetabolism related to ineffective erythropoiesis. Children with the beta-thalassemia major who are transfusion dependent can develop signs and symptoms suggestive of neuropathies, paralysis, iron overloads such as ascites, spider nevi or hepatomegaly. Heart failure and palpitations can be seen in children with severe anemia.

# alleles affected	Genotype	Name	Description
<b>α-Thalassemia</b>			
1	-/α α/α	Alpha thalassemia minima	Silent gene carrier

2	$\alpha/\alpha$ $-/-$	Alpha thalassemia minor	More in Asians Mild microcytic anemia
3	$\alpha/-$ $\alpha/-$	Alpha thalassemia minor	More in Africans Mild microcytic anemia
4	$-/-$ $-/\alpha$	Hemoglobin H disease	Microcytic anemia Hepatosplenomegaly
5	$-/-$ $-/-$	Alpha thalassemia major	Edematous newborn Stillborn: "Hydrops fetalis"
<b><math>\beta</math>-Thalassemia</b>			
1	$\beta^+/\beta$ or $\beta/\beta$	Beta thalassemia minor	Microcytic anemia
2	$\beta/\beta^+$ or $\beta^+/\beta^+$	Beta thalassemia intermedia	Microcytic anemia Occasional transfusions
3	$\beta/\beta$	Beta thalassemia major	Severe anemia, hepatosplenomegaly, iron overload, bone deformities, death by the age of 20

## Diagnostic Workup for Thalassemia in Children

The first cue towards the possibility of thalassemia in a child with anemia usually comes from the complete blood count. Patients with **severe thalassemia usually have a hemoglobin level below 8 g/dL**. The mean corpuscular volume and mean corpuscular Hb are usually very low in children with thalassemia, compared to children with hypochromic microcytic anemia due to iron deficiency. Patients with **beta-thalassemia major usually have elevated white blood cell count** which results from miscounting larger nucleated red blood cells like white blood cells.

Peripheral blood smears usually reveal **hypochromasia, microcytosis, nucleated red blood cells, basophilic stippling and the presence of immature leukocytes**.

Hb electrophoresis usually shows **elevated levels of fetal hemoglobin, HbA2 and the presence of abnormal hemoglobins**, as previously described in the pathophysiology section.

**Iron studies** should be performed in children who are transfusion dependent for the early detection of iron overload. Serum ferritin levels are usually elevated in children who are transfusion dependent, which correlates with the degree of iron overload.

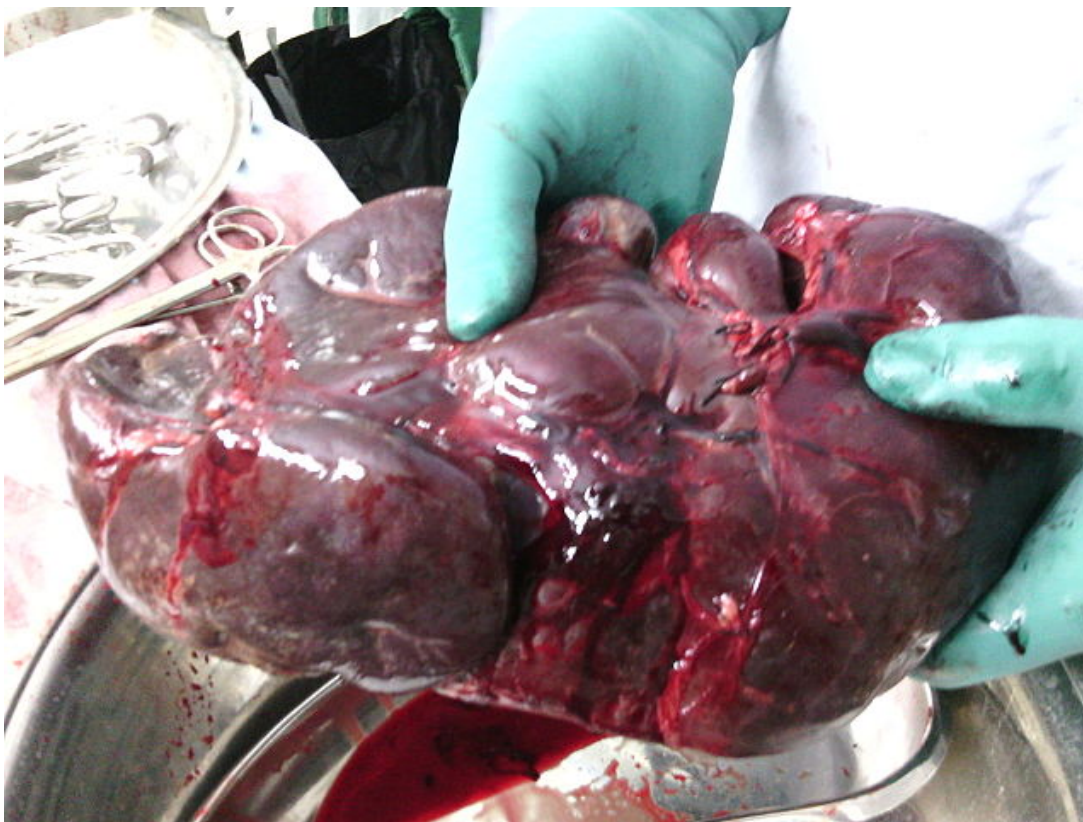
Children who do not receive regular blood transfusions can have a widening of the erythroid marrow space within the bones which is encountered as early osteoporotic changes on skeletal x-rays. Maxillary overbite due to maxilla overgrowth can be seen on skull x-rays of children with beta-thalassemia major.

Children with palpitations or other signs and symptoms suggestive of heart failure should undergo a **chest x-ray and echocardiography** to assess the size and function of the heart respectively.

**Magnetic resonance imaging** is useful in the assessment of iron overload in the liver or the heart.

## Treatment of Thalassemia in Children

**Splenectomy is usually needed in most children with severe forms of thalassemia.** After splenectomy, children usually show improved red blood cell indices. The most important indication for splenectomy in children with thalassemia is the **requirement of more than 250 ml/kg of packed red blood cells per year** to maintain a hemoglobin level of more than 10 g/dL.



**Image:** "Surgically removed spleen of a thalassemic child. It is about 15 times larger than normal." by Almazi.  
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**Bone marrow transplantation** can be used to cure the condition in children who have been diagnosed recently with beta-thalassemia major, and who did not receive a significant number of blood transfusions. When bone marrow transplantation is planned, **adequate human leukocyte antigen typing** is needed to prevent graft rejection or graft versus host disease.

Children who are dependent on repeated and regular blood transfusions should receive an **iron chelating agent** to prevent the deposition of excessive iron within internal organs, such as the liver and the heart. The most commonly used chelating agents are deferoxamine mesylate and deferasirox. Children who are allergic to deferoxamine mesylate should receive corticosteroids injections at the site of the injection of the chelating agent.



**Febrile reactions to blood transfusions are common** in children with beta-thalassemia major, and the administration of acetaminophen before blood transfusion can lower the risk of this complication.

Children who receive a splenectomy should be **vaccinated against encapsulated organisms**. Pneumococcal polyvalent, haemophilus influenza type b and pneumococcal conjugate vaccines should be administered.

<b>α thalassemia minima &amp; minor β thalassemia minor</b>	<b>Hemoglobin H β thalassemia intermedia</b>	<b>β thalassemia major</b>	<b>α thalassemia major</b>
<ul style="list-style-type: none"> <li>• Folate</li> </ul>	<ul style="list-style-type: none"> <li>• Folate</li> <li>• Periodic transfusions</li> </ul>	<ul style="list-style-type: none"> <li>• Transfusion q 2-3 wks</li> <li>• Deferoxamine (to chelate excess iron)                             <ul style="list-style-type: none"> <li>• Transplant if severe</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• In utero transfusions</li> <li>• Bone marrow transplant</li> </ul>

## Prognosis of Thalassemia in Children

Alpha thalassemia is highly mortal disease. Fetuses born with this disease develop hydrops foetalis.

In patients with beta thalassemia morbidity and mortality depend on the severity of the disease and management provided. Severe cases are fatal if treatment is not provided. Common cause of death are:

- Organ failure due to iron overload
- Cardiac failure due to severe anemia
- Liver diseases
- Due to complications of treatment like severe infections from transfusions.
- Massive splenomegaly

## References

[Pediatric Thalassemia. Practice Essentials, Background, Pathophysiology.](#) via emedicine.medscape.com

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