Prevention & Management of Infections in Thalassemia

Cooley's Anemia Foundation
Patient-Family Conference 2017

Erica Esrick, MD
Dana-Farber / Boston Children's
Cancer and Blood Disorders Center

DANA-FARBER Boston Children's
CANCER AND BLOOD DISORDERS CENTER

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Erica Esrick Disclosures

- Research support to my institution
  - Celgene, bluebird bio

Why are infections more likely in thalassemia patients?

- Decreased innate immunity
- Iron overload
- Iron chelation therapy
- Transfusion-related infections
- Splenectomy
- Central venous catheters
- Stem cell transplantation

Why are infections more likely in thalassemia patients?

- Decreased innate immunity
- Iron overload
- Iron chelation therapy
- Transfusion-related infections
- Splenectomy
- Central venous catheters
- Stem cell transplantation

Why are infections more likely in thalassemia patients?

- Decreased innate immunity
  - Changes in number of T and B cells and immunoglobulins
  - Neutrophils may have decreased function
  - Ongoing area of investigation…. *Blood* Journal June 2017:

Reduced PU.1 expression underlies aberrant neutrophil maturation and function in β-thalassemia mice and patients

Panjaree Siwaponanan,[1-3] Jurre Ynze Siegers,[1] Razi Ghazali,[1] Thian Ng,[1,4] Bradley McColl,[1] Garrett Zhen-Wei Ng,[1,5] Philip Sutton,[1,5,6] Nancy Wang,[4] Isabelle Ooi,[1,4] Chayada Thiengtavor,[7] Suthat Fucharoen,[2] Pornthip Chaichompoo,[7] Saovaros Svasti,[2,8] Odilia Wijburg,[4] and Jim Vadolas[1,6]

Vento et al. Lancet Infect Dis 2006; 6: 226-33.

Why are infections more likely in thalassemia patients?

- Decreased innate immunity
- Iron overload
- Iron chelation therapy
- Transfusion-related infections
- Splenectomy
- Central venous catheters
- Stem cell transplantation

Iron and infection

All living things need iron to grow!

Fe^{3+}

Some bacteria become more virulent (stronger, more toxic) in the presence of high iron levels:

Yersinia, Klebsiella, E. coli, Streptococcus, Pseudomonas, Listeria, Legionella

High iron levels can also cause inflammation and impair the immune response to infection.

→ How to help? CHELATE!

But….

Why are infections more likely in thalassemia patients?

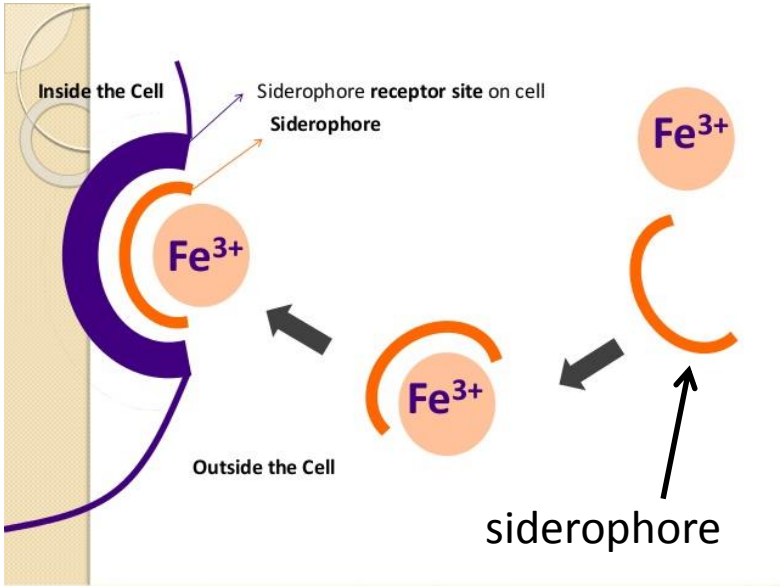
- Decreased innate immunity
- Iron overload
- Iron chelation therapy
- Transfusion-related infections
- Splenectomy
- Central venous catheters
- Stem cell transplantation

Chelation and infection

Deferoxamine (Desferal)

Some bacteria make **siderophores** to capture iron.(Siderophore = “iron carrier”)

Deferoxamine (Desferal) is a siderophore made by *Streptomyces.*



Deferoxamine can increase the risk of infections with:

- Bacteria (especially Yersinia species)
- Fungus (mucormycosis)

What to do? Stop Desferal with every fever until further evaluation.

Chelation and infection:

Deferiprone (Ferriprox) – risk of agranulocytosis

FERRIPROX® (deferiprone) tablets, for oral use
Initial U.S. Approval: 2011

WARNING: AGRANULOCYTOSIS/NEUTROPENIA

See full prescribing information for complete boxed warning.

- **Ferriprox can cause agranulocytosis that can lead to serious infections and death. Neutropenia may precede the development of agranulocytosis. (5.1)**
- **Measure the absolute neutrophil count (ANC) before starting Ferriprox and monitor the ANC weekly on therapy. (5.1)**
- **Interrupt Ferriprox if infection develops and monitor the ANC more frequently. (5.1)**
- **Advise patients taking Ferriprox to report immediately any symptoms indicative of infection. (5.1)**

<u>Package insert reports:</u>

Neutropenia in 6.2%
Agranulocytosis in 1.7%

What to do? Check weekly absolute neutrophil count (ANC). Stop chelation with fever / signs of infection.

Chelation and infection

Deferasirox (Jadenu and Exjade)

Less clear association with infection

Cytopenias (low blood counts) have been reported.

What to do? (Less clear)
Stop chelator with fever or low blood counts.

Why are infections more likely in thalassemia patients?

- Decreased innate immunity
- Iron overload
- Iron chelation therapy
- Transfusion-related infections
- Splenectomy
- Central venous catheters
- Stem cell transplantation

Transfusion-related infections

	Examples
Viral	HIV Hepatitis B Hepatitis C HTLV West Nile Virus Zika virus
Bacterial	Syphilis Gram-negative (ie, Yersinia, Serratia)
Parasitic	Babesia Plasmodium (malaria) Trypanosoma cruzi (Chagas disease)

Transfusion-related infections: How do we try to prevent them?

Donor screening	Check pulse, temperature, and BP

✓

Transfusion-related infections: How do we try to prevent them?

Donor screening	Check pulse, temperature, and BP
Donor screening	Donor questionnaire

✓

DONOR HEALTH QUESTIONNAIRE asks about:

Behaviors that may increase risk for HIV, HCV, HBV

Signs of current bacterial infection in donor

ARE YOU (#1-3)
1. Feeling healthy and well today?
2. Currently taking an antibiotic?
3. Currently taking any other medication for an infection?

IN THE PAST 12 MONTHS HAVE YOU (#11-26)	
11. Had a blood transfusion?	
12. Had a transplant such as organ, tissue, or bone marrow?	
13. Had a graft such as bone or skin?	
14. Come into contact with someone else's blood?	
15. Had an accidental needle-stick?	
16. Had sexual contact with anyone who has HIV/AIDS or has had a positive test for the HIV/AIDS virus?	
17. Had sexual contact with a prostitute or anyone else who takes money or drugs or other payment for sex?	
18. Had sexual contact with anyone who has ever used needles to take drugs or steroids, or anything not prescribed by their doctor?	
19. **Male donors**: Had sexual contact with another male? (Female donors check "I am female.")	☐ I am female
20. **Female donors**: Had sexual contact with a male who had sexual contact with another male in the past 12 months? (Males: check "I am male.")	☐ I am male
21. Had sexual contact with a person who has hepatitis?	
22. Lived with a person who has hepatitis?	
23. Had a tattoo?	
24. Had ear or body piercing?	
25. Had or been treated for syphilis or gonorrhea?	
26. Been in juvenile detention, lockup, jail, or prison for more than 72 consecutive hours?	

DONOR HEALTH QUESTIONNAIRE asks about:

Relevant travel history
(Malaria, mad cow disease)

IN THE PAST THREE YEARS HAVE YOU
27. Been outside the United States or Canada?
FROM 1980 through 1996 (#28-29)
28. Did you spend time that adds up to three (3) months or more in the United Kingdom? (Review list of countries in the UK in the Required Materials for All Donors book)
29. Were you a member of the U.S. military, a civilian military employee, or a dependent of a member of the U.S. military?
FROM 1980 TO THE PRESENT, DID YOU (#30-31) (See Required Materials for All Donors book)
30. Spend time that adds up to five (5) years or more in Europe? (Review List of countries in Europe)
31. Receive a blood transfusion in the United Kingdom or France? (Review list of countries in the UK.)

Transfusion-related infections: How do we try to prevent them?

Donor screening	Check pulse, temperature, and BP
Donor screening	Donor questionnaire
Preparation of blood units	Leuko-reduction: reduces risk of CMV and possibly other infections.

✓

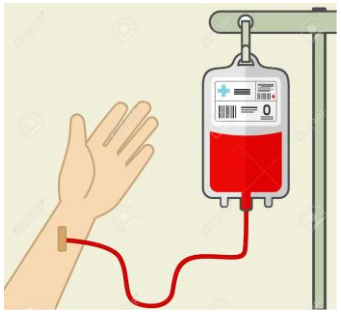
✓

✓

Transfusion-related infections: How do we try to prevent them?

Donor screening	Check pulse, temperature, and BP	✓
Donor screening	Donor questionnaire	✓
Preparation of blood units	Leuko-reduction: reduces risk of CMV and possibly other infections.	✓
Test donated blood	Remove small volume of blood and test for: HIV, HBV, HCV, HTLV, syphilis, West Nile Virus, Chagas disease, and babesia	✓

Transfusion-related infections: How do we try to prevent them?

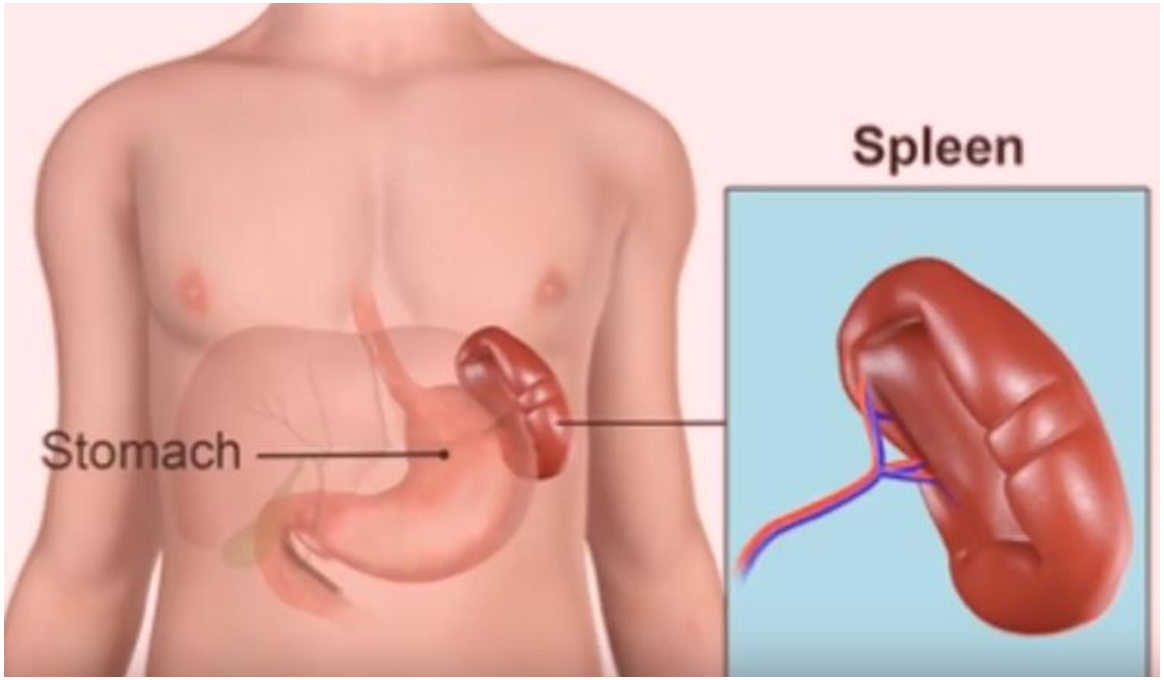


Donor screening	Check pulse, temperature, and BP	✓
Donor screening	Donor questionnaire	✓
Preparation of blood units	Leuko-reduction: reduces risk of CMV and possibly other infections.	✓
Test donated blood	Remove small volume of blood and test for: HIV, HBV, HCV, HTLV, syphilis, West Nile Virus, Chagas disease, and babesia	✓
Storage of blood units	Cool temperature decreases the risk of bacterial growth	✓

Why are infections more likely in thalassemia patients?

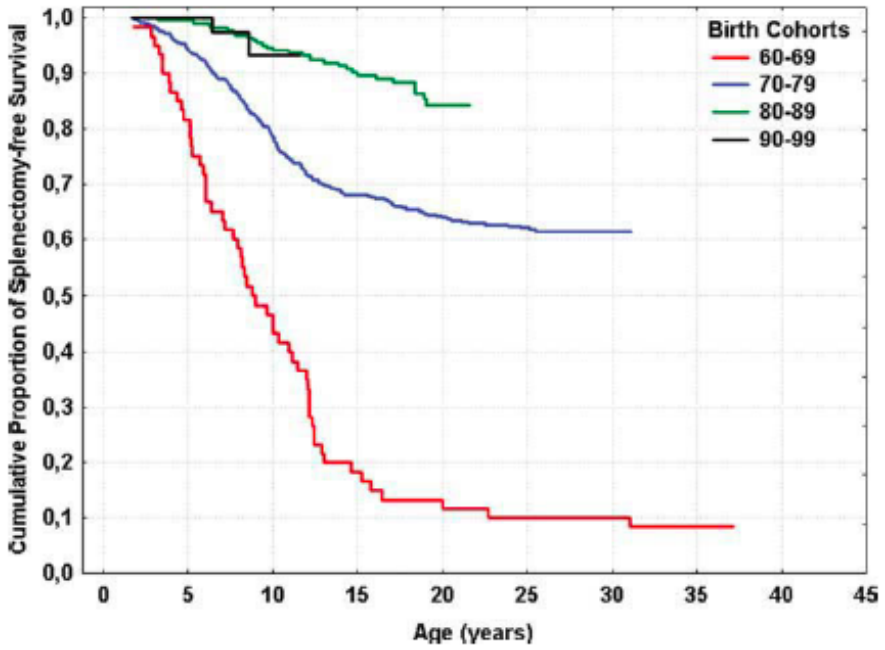
- Decreased innate immunity
- Iron overload
- Iron chelation therapy
- Transfusion-related infections
- Splenectomy
- Central venous catheters
- Stem cell transplantation

The spleen



- Filters blood: Removes damaged RBCs, removes bacteria
- Makes blood cells:
  - Lymphocytes (good!) – Immune protection
  - RBCs (bad!) – Sign of ineffective erythropoiesis

The spleen in thalassemia



Piga et al. AJH 2011

- Can become enlarged from ineffective erythropoiesis
- Splenomegaly can cause increased transfusion requirement
- Splenectomy can decrease transfusion volumes:
  - less common over time
- INFECTION RISK: Post-splenectomy risk of severe bacterial infection, especially with encapsulated bacteria

Asplenic sepsis: Prevention

1. **Vaccines:** Ideally at least 2 weeks before surgery

Bacteria	Vaccines to protect
Streptococcus pneumoniae	PCV-13 series PPSV-23
Haemophilus influenzae "H. flu" (not "the flu", which is influenza virus)	Hib series
Neisseria meningitidis	MCV series (Menactra, Menveo) ** MenB series (newer)

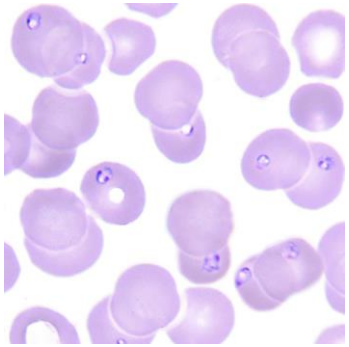
2. Prophylactic daily antibiotic: usually penicillin

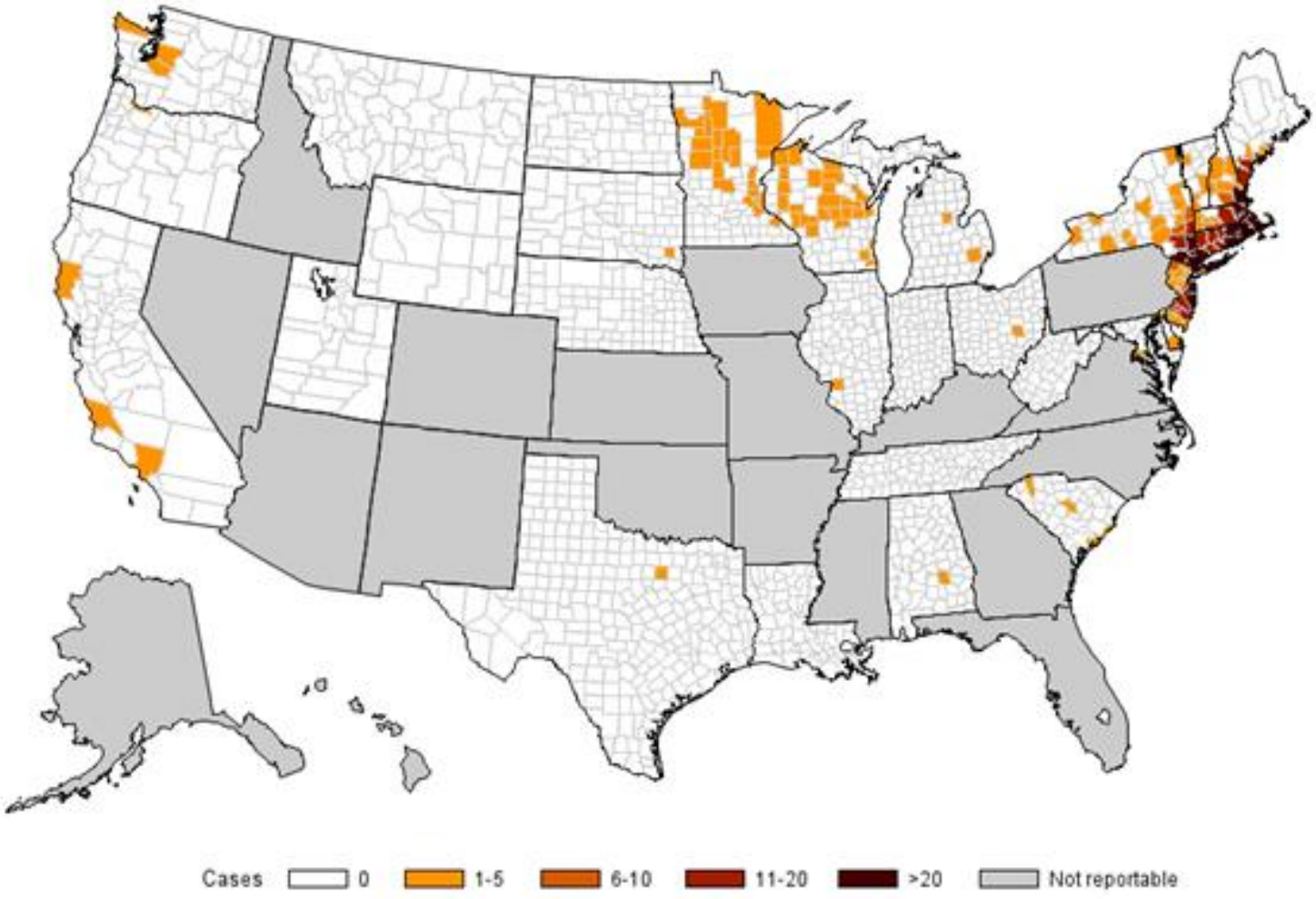
3. Antibiotics on hand

Asplenic sepsis: Management

- Always inform medical staff about asplenic status
- Immediate ER visit
- Immediate broad-spectrum IV antibiotics:
  - ie, ceftriaxone + vancomycin

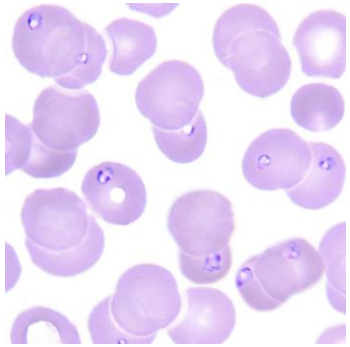
Babesiosis





https://www.cdc.gov/parasites/babesiosis/data-statistics/maps/maps.html

Babesiosis



- Acquired by tick bite or blood transfusion
- Symptoms at 1-6 weeks after tick bite
- Asplenia = higher risk for severe illness
- RBC lysis → Fever, fatigue, malaise, weakness

Why are infections more likely in thalassemia patients?

- Decreased innate immunity
- Iron overload
- Iron chelation therapy
- Transfusion-related infections
- Splenectomy
- Central venous catheters
- Stem cell transplantation

Why are infections more likely in thalassemia patients?

- Decreased innate immunity
- Iron overload
- Iron chelation therapy
- Transfusion-related infections
- Splenectomy
- Central venous catheters
- Stem cell transplantation

What to do?

- Optimize chelation
- No spleen?
  - Antibiotics!
  - Vaccines
- Stop chelation with fever
- Safe blood supply