IRON & IRON OVERLOAD

Saturday, November 28, 2020

Cyrus C. Hsia, HBSc, MD, FRCPC
Associate Professor of Medicine,
Schulich School of Medicine and Dentistry, Western University
Associate Medical Director, Blood Transfusion Laboratory
London Health Sciences Centre

WELCOME

- Welcome to London, Ontario

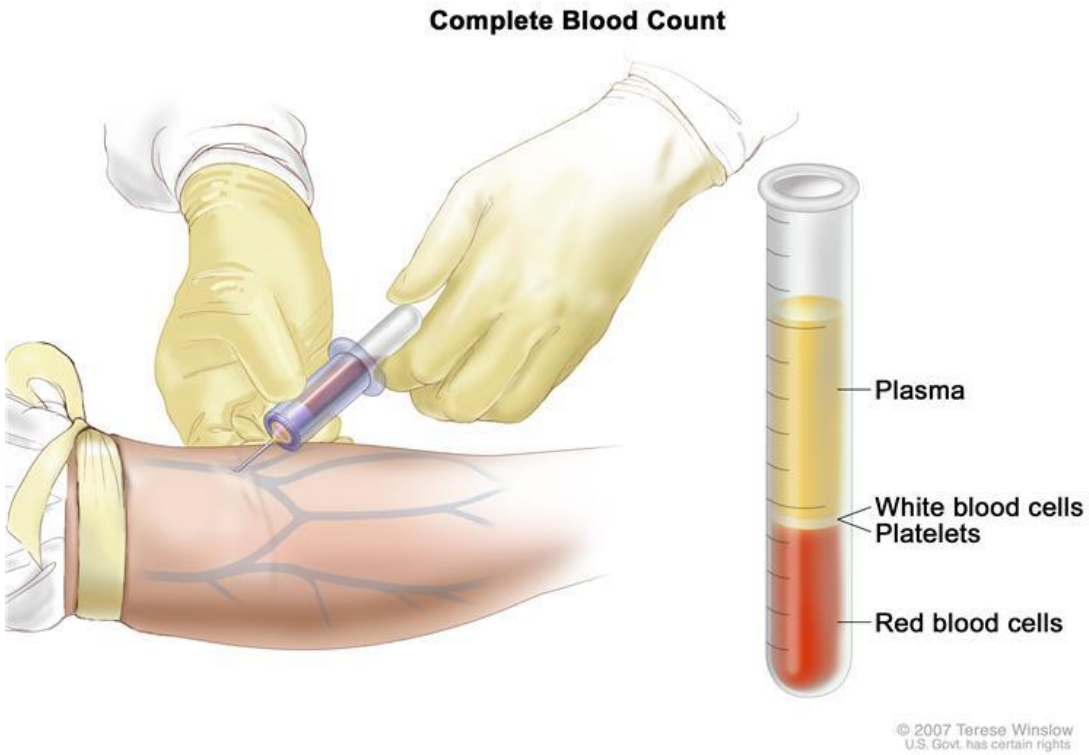
London
CANADA

OBJECTIVES

- At the conclusion of this presentation the participant will be able to:
  - 1. Understand the importance of iron in the body
  - 2. Review the toxicity of iron to organs as a result of chronic red blood cell transfusions
  - 3. Review the Iron Overload management in conditions such as myelodysplastic syndrome (MDS)

SOME BASICS

To iron or not to iron…

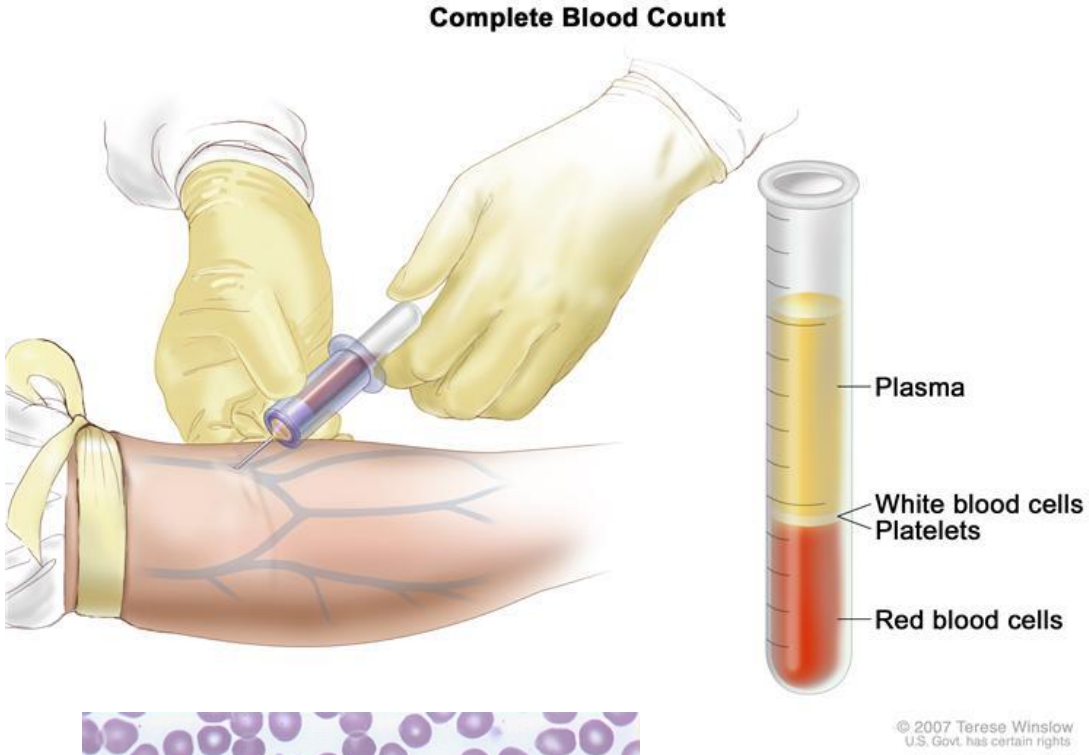


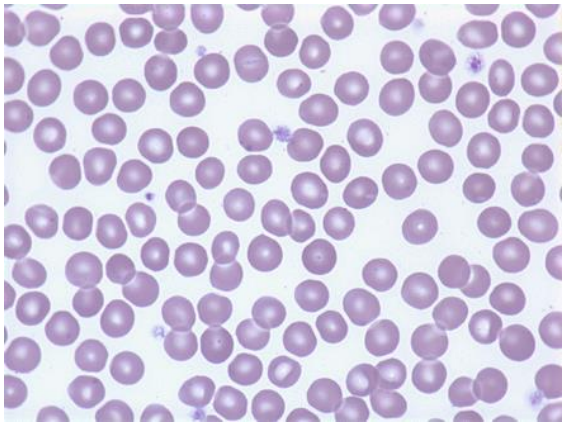
CBC

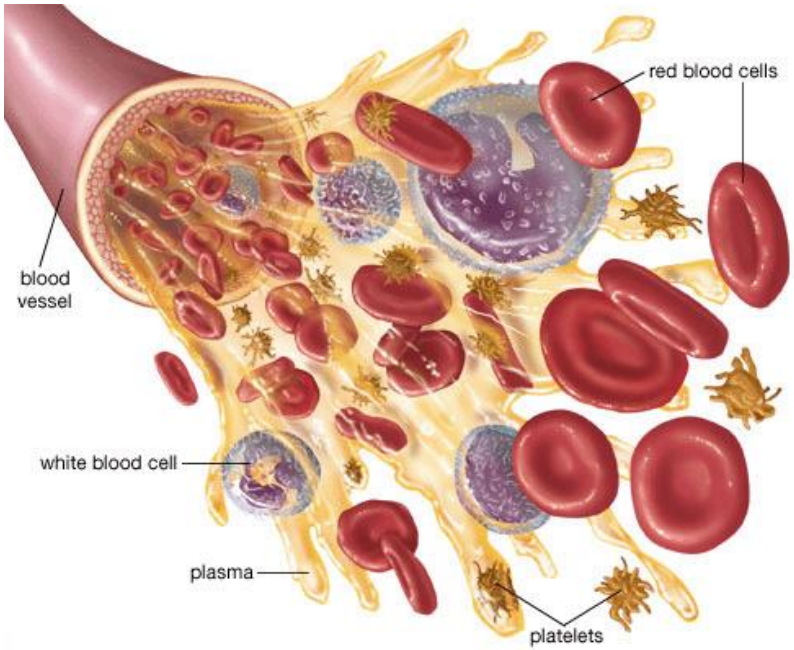
The complete blood count

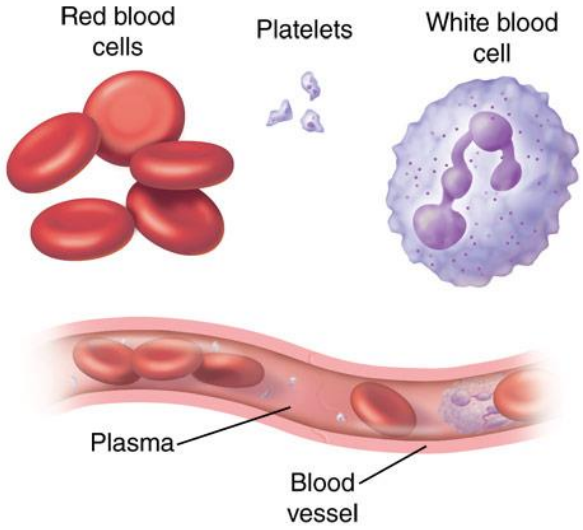
CBC

The complete blood count



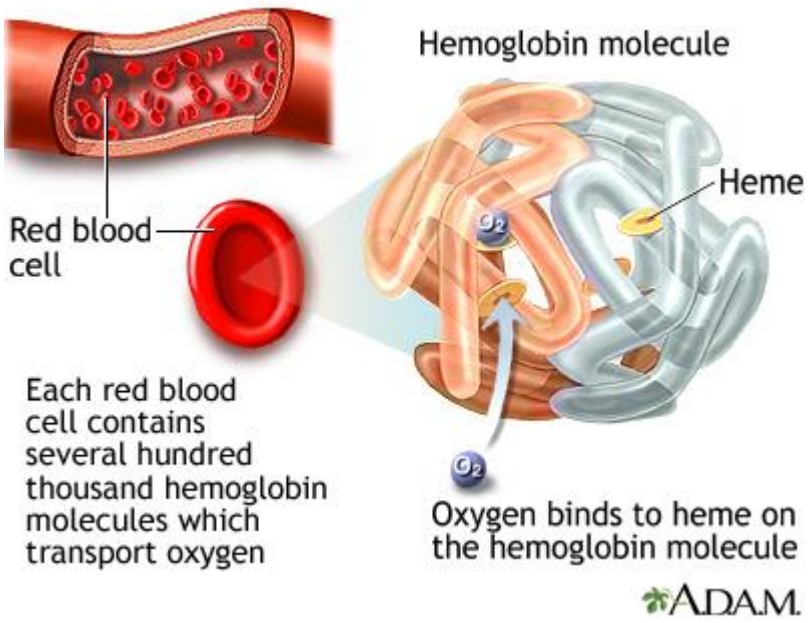






BLOOD

What is blood made of?



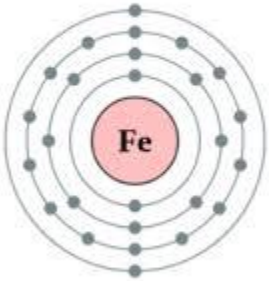
RBC

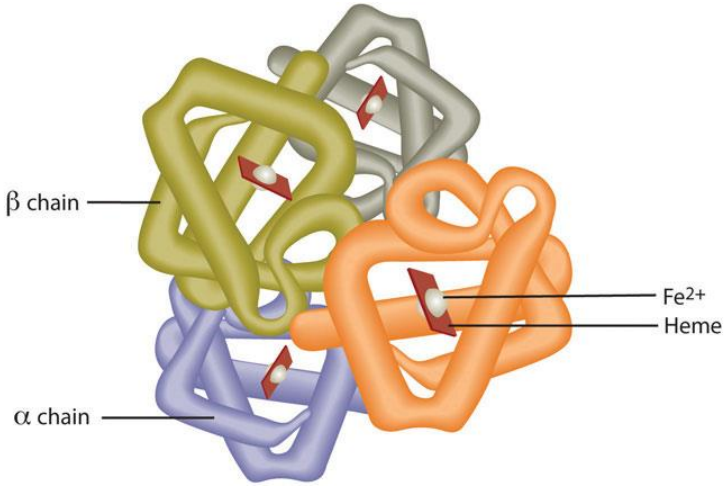
Red blood cells (RBC)

Hemoglobin molecules are essential.. They carry oxygen in the red blood cells.

Each heme ring contains an iron atom

26: Iron 2,8,14,2



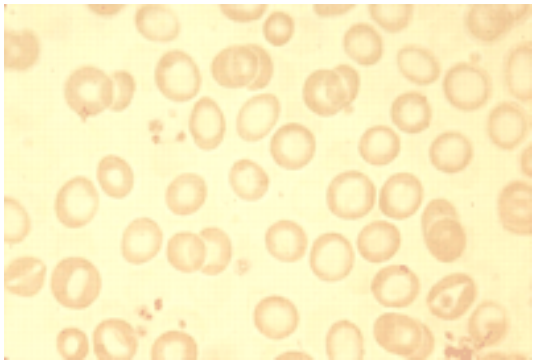


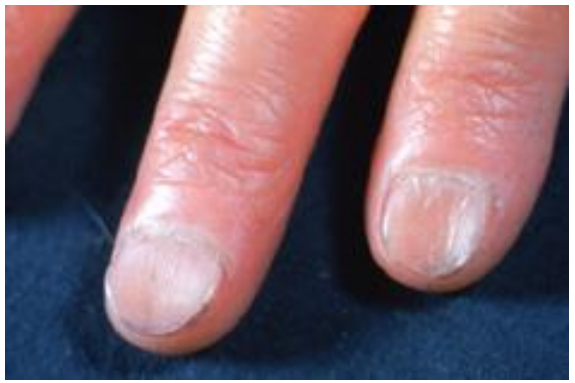
IRON

Iron is essential for hemoglobin

TOO LITTLE IRON

- **Clinical Features of Iron Deficiency Anemia**
- Anemia in general
  - Fatigue (tired), shortness of breath, chest pain, palpitations, generally feel weak
- Specific to iron deficiency anemia
  - Sore tongue, difficulty swallowing, brittle or spoon shaped nails, and cravings for ice or dirt





TOO LITTLE IRON

IS MORE IRON BETTER?

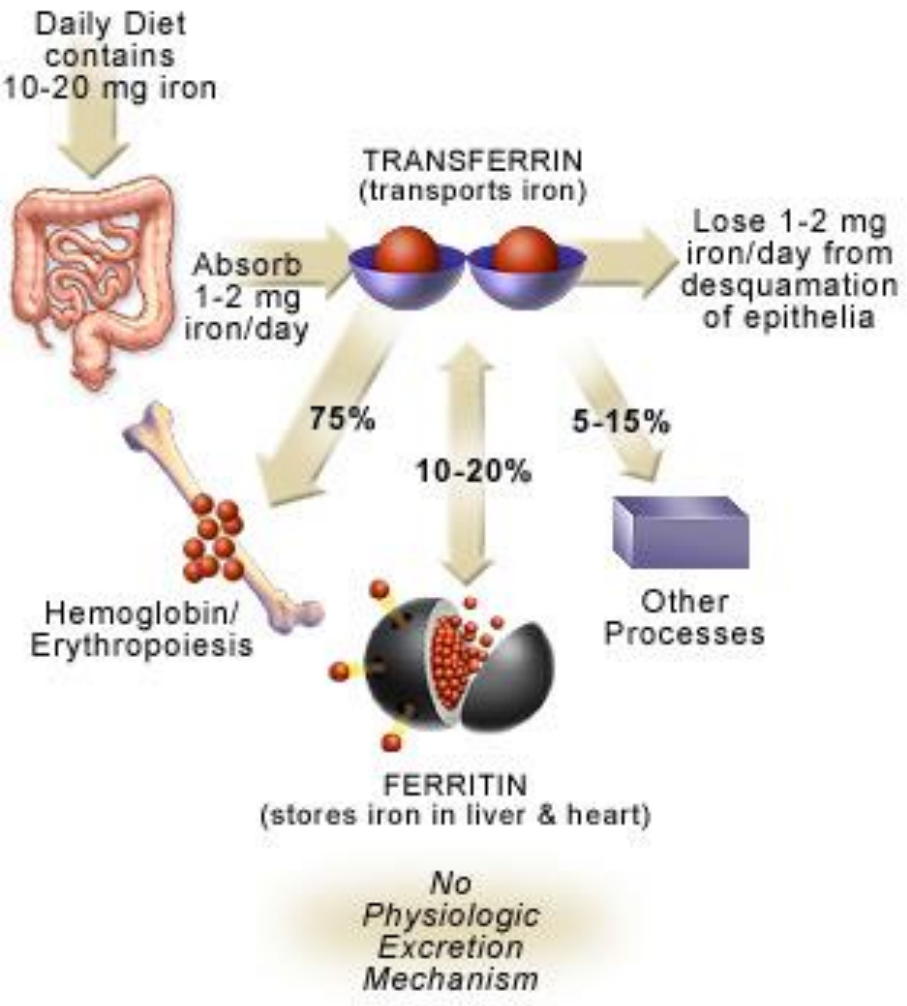
TOO MUCH IRON!

BASIC PHYSIOLOGY

Iron Metabolism & Regulation

Nov 28, 2020 C. Hsia

IRON ABSORPTION AND METABOLISM



Normal Iron Absorption and Storage.
http://www.cdc.gov/ncbddd/hemochromatosis/training/pathophysiology/iron_cycle_popup.htm

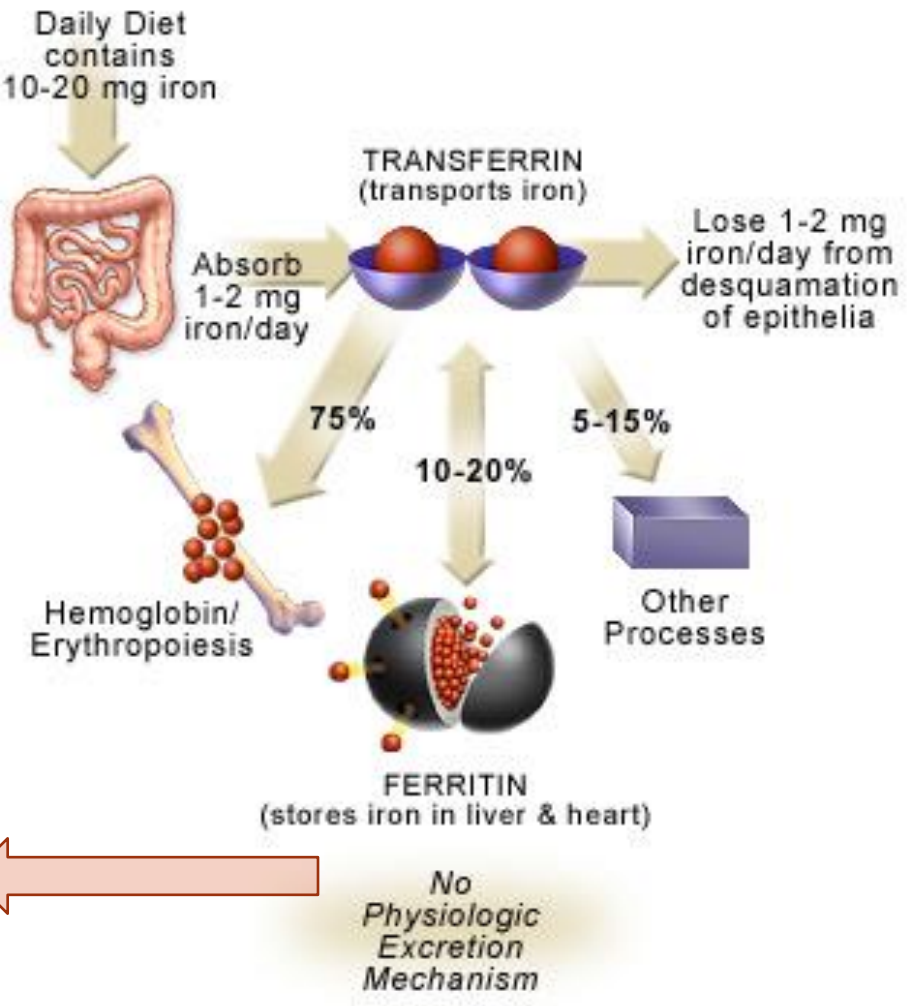
DIETARY IRON

- Average North American diet provides 10-30 mg iron in 2 forms – heme and non-heme iron
  - Heme iron from meat and fish
  - Non-heme iron vegetables and fortified cereal

DIETARY IRON

- Average North American diet provides 10-30 mg iron in 2 forms – heme and non-heme iron
  - Heme iron from meat and fish
  - Non-heme iron vegetables and fortified cereal
- Absorption in the small intestines (~1-2mg)
- Daily dietary requirements
  - 1-2 mg usually sufficient
  - Increased requirements for – pregnancy, menstruation, breastfeeding

IRON ABSORPTION AND METABOLISM



- Because we cannot control how much iron is excreted, the balance of iron of depends on how much iron goes into the body.

Normal Iron Absorption and Storage.
http://www.cdc.gov/ncbddd/hemochromatosis/training/pathophysiology/iron_cycle_popup.htm

IRON IN MDS

Myelodysplastic Syndromes

Nov 28, 2020 C. Hsia

MYELODYSPLASTIC SYNDROMES

- Definition
  - Myelodysplastic syndromes (MDS) form a group of clonal hematopoietic stem cell malignancies characterized by ineffective hematopoiesis in one or more cell lineages, associated peripheral cytopenias, and risk of transformation to acute myeloid leukemia

Sloand EM. Myelodysplastic syndromes: introduction. Semin Hematolo. 2008;45:1-2. Valent P, Horny HP, Bennett JM, et al. Leuk Res 2007;31:72-36.

Dr. Robert Barr and the Ford Pinto

MYELODYSPLASTIC SYNDROMES

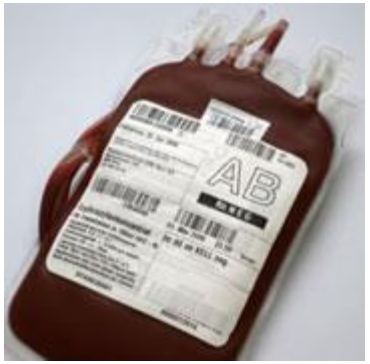
- In other words..
  - MDS is a group of blood and bone marrow disorders (cancers) where the blood cells are made with defects and don’t survive as long as it should.
  - This leads to low blood counts in 1 or more of the blood cells.
  - It is NOT leukemia, but can be considered pre-leukemic.
  - It is NOT 1 disease and behaves differently in different people.

IMPACT OF MDS

- Patient
  - Poor quality of life - time and commitment to transfusions
  - Complications of Iron Overload
  - Cardiorespiratory symptoms
  - Hospitalizations for cardiac complications, infections, bleeding, increased risk of leukemic transformation
  - Increased risk of shorter survival
- Society
  - Transfusion burden
  - Hospitalizations for cardiac complications, infections, complications of iron overload, bleeding, leukemia

MANAGEMENT FOR MDS PATIENTS

- The mainstay of management is supportive
- Transfusions, antibiotics
  - No specific transfusion threshold, rather patient dependent based on level of hemoglobin associated with symptoms of anemia



Steensma DP and Bennett JM. The Myelodysplastic Syndromes: Diagnosis and Treatment. Mayo Clin Proc. 2006;81(1):104-130.

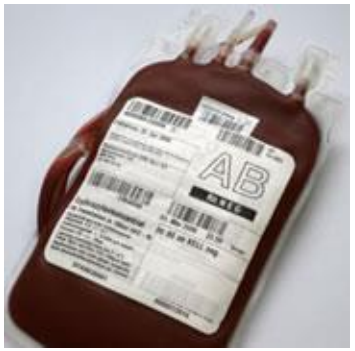
TOO MUCH IRON

Iron overload affect on organs

Nov 28, 2020 C. Hsia

WHY DO MDS PATIENTS DEVELOP TOO MUCH IRON?

- Each unit of packed RBC (red blood cell) contains about 250mg of iron!
  - 2 units = 500mg
  - 10 units = 2500mg
  - 20 units = 5000mg



- Recall that the daily amount of iron lost in the body is only 1-2mg and the total body iron is 3000-5000mg.

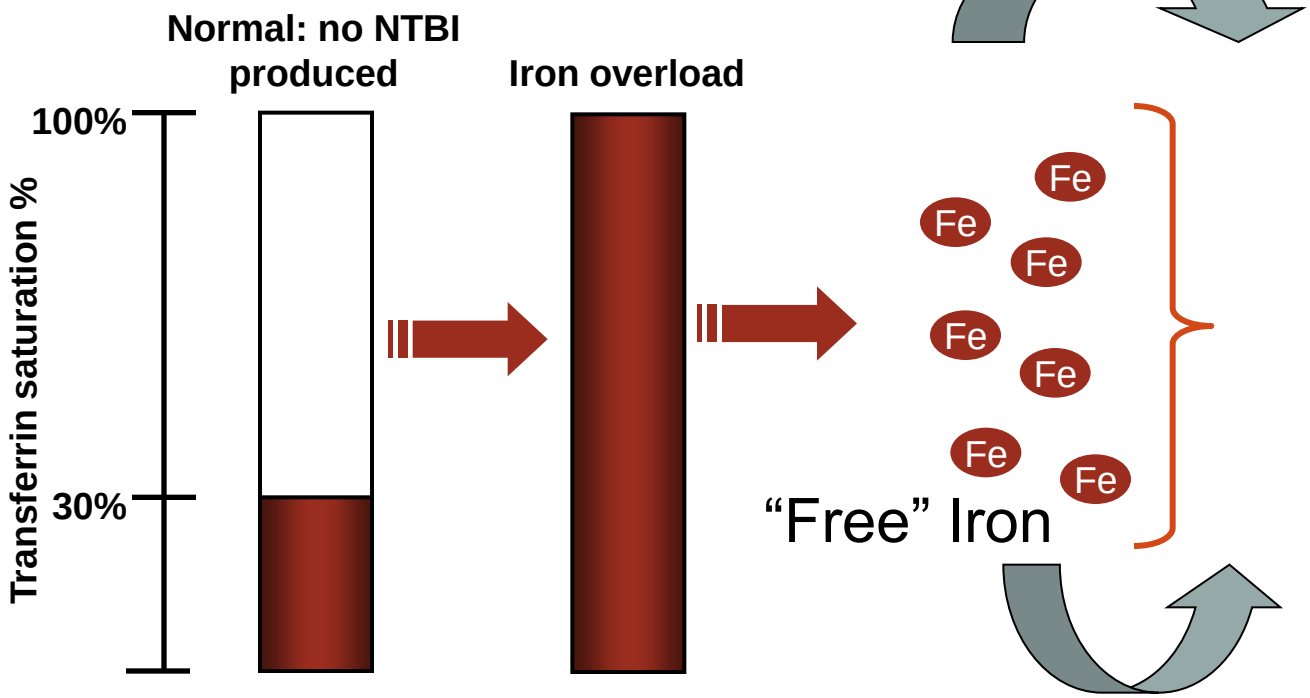
Steensma DP and Bennett JM. The Myelodysplastic Syndromes: Diagnosis and Treatment. Mayo Clin Proc. 2006;81(1):104-130.

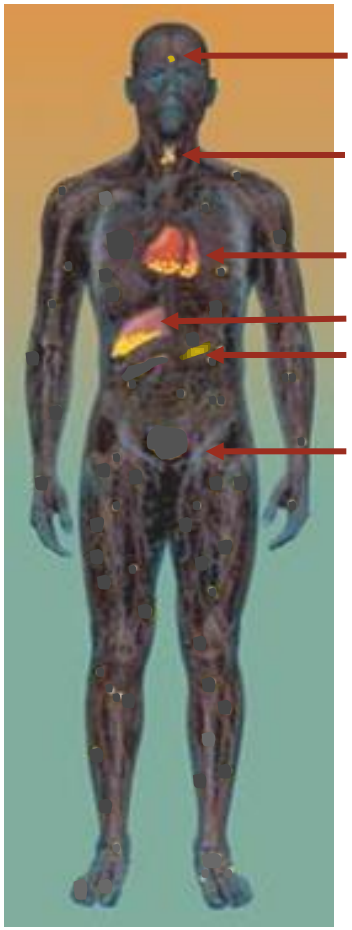
FREE IRON: THE ESSENCE OF IRON OVERLOAD

Saturation of transferrin due to
- **Frequent blood transfusions, and**
- **Ineffective erythropoiesis leading to increased iron absorption**

Subsequent formation of NTBI in plasma

Uncontrolled iron loading of organs



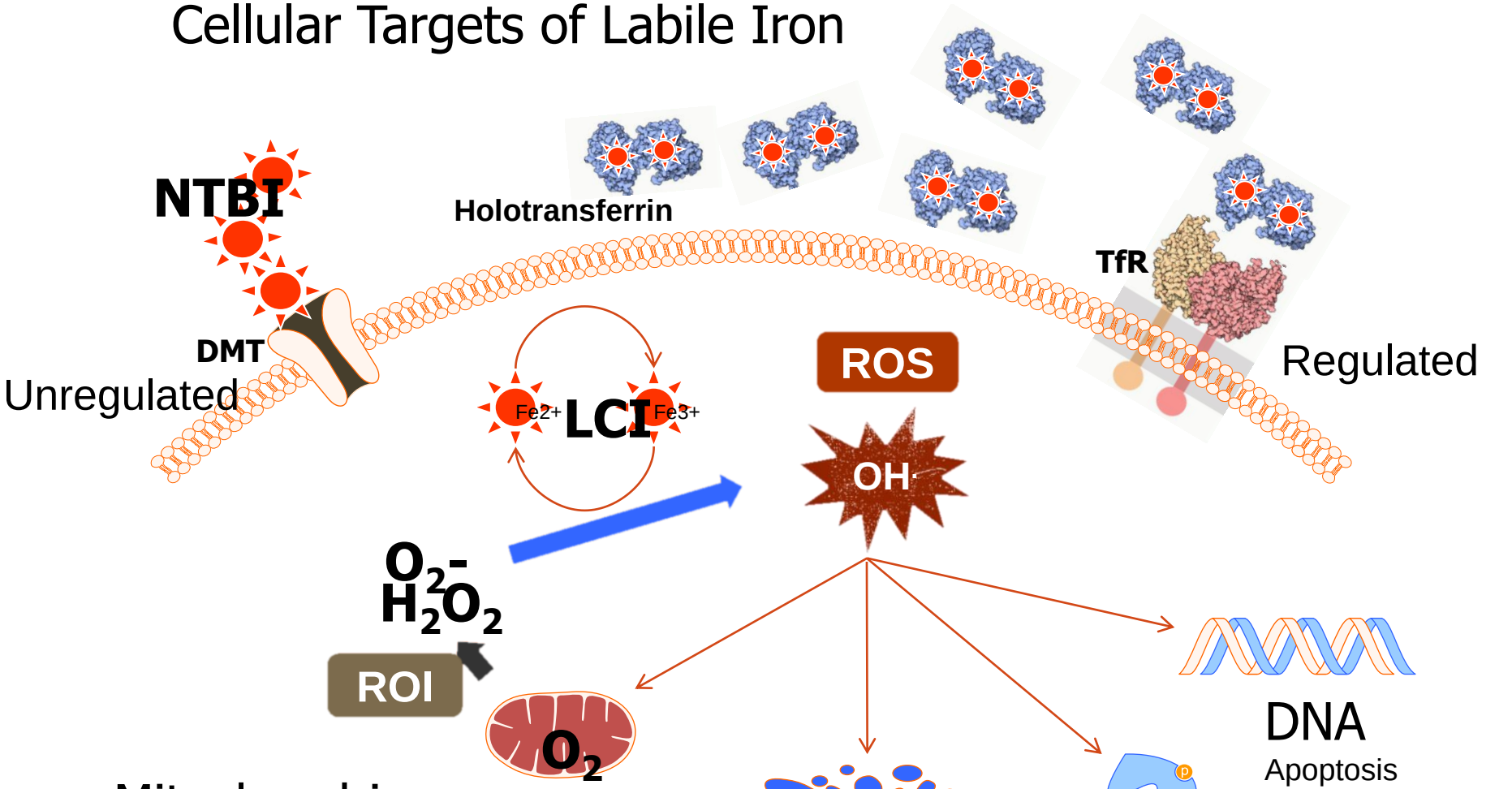


NTBI – non-transferrin-bound iron

Nov 28, 2020 C. Hsia

As presented by R. Wells at CCMDS 2012, Montreal.

Cellular Targets of Labile Iron



Mitochondria

Inefficient energy metabolism
Apoptosis
Senescence

DMT-Divalent metal transporter
TfR-Transferrin receptor
ROI-reactive oxygen intermediates
ROS-reactive oxygen species

Lipid

Membrane damage
Cell lysis

Protein

Altered signaling
Proliferation
Fibrosis

DNA

Apoptosis
Mutagenesis

As presented by R. Wells at CCMDS 2012, Montreal.

HOW TO ASSESS

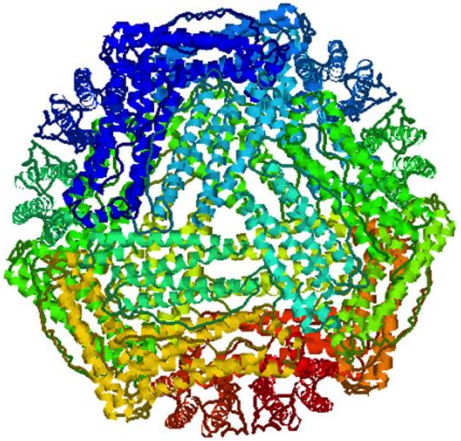
How to assess for iron overload

Nov 28, 2020 C. Hsia

METHODS TO ASSESS IRON OVERLOAD

- Blood tests
  - Serum ferritin
  - Transferrin saturation
- Liver iron concentration (LIC)
  - Liver biopsy
  - Hepatic magnetic resonance imaging (MRI); FerriScan®
  - Superconducting quantum interference device (SQUID)
- Cardiac iron concentration
  - Cardiac MRI

SERUM FERRITIN



Pros	Cons
• Inexpensive and easily measured • Allows for frequent monitoring • Positive correlation with morbidity and mortality	• Indirect measurement of iron burden • Requires serial measurements and/or combination with other indicators of iron overload • Levels are influenced by many factors, including infection and inflammation

Normal	Mild-to-moderate iron overload	Severe iron overload
< 300 µg/L	> 1,000-< 2,500 µg/L	> 2,500 µg/L

TRANSFERRIN SATURATION

- May be useful as a complement to serum ferritin for the diagnosis of iron overload
- Normal levels of transferrin saturation: 20% to 50%
  - Transferrin saturation > 50% is indicative of an iron-overload

Limitations[2,3]

- Not useful for monitoring long-term trends in iron burden
- Unable to detect iron overload caused primarily by the reticuloendothelial system
- Not as reliable as LIC in estimating total body iron stores

TIBC, total iron-binding capacity; UIBC, unbound iron-binding capacity; LIC, liver iron concentration

1. Mazza J. Manual of clinical hematology. Philadelphia: Lippincott Williams & Wilkins, 2002;129.
2. Gattermann N, et al. Hematol Oncol Clin North Am. 2005;19 Suppl 1:18-25.
3. Santini V, et al. Leuk Res. 2010;34:1576-1588

TRANSFUSION HISTORY AND SURROGATE MARKERS

- **Number of units of transfused blood**
  - No prospectively validated threshold has been established
  - Published recommendations, based on expert opinion, suggest a threshold of 25 to 50 units
  - Should not be the sole index of iron burden in MDS
    - Some patients (i.e., RARS) have elevated serum ferritin levels regardless of transfusion history and may benefit from initiation of iron chelation before an arbitrary number-of-units threshold has been reached
- **Serum ferritin levels**
  - In the literature, experts have recommended a threshold ranging from 1000 to 2500 μg/L
  - May be affected by inflammation
    - Interpretation of ferritin measurements in the context of fasting transferrin saturation is strongly recommended
  - Iron chelation should not be started unless transferrin saturation exceeds >0.5 (50%)

Wells RA, et al. *Leuk Res.* 2008 Sep;32(9):1338-1353.

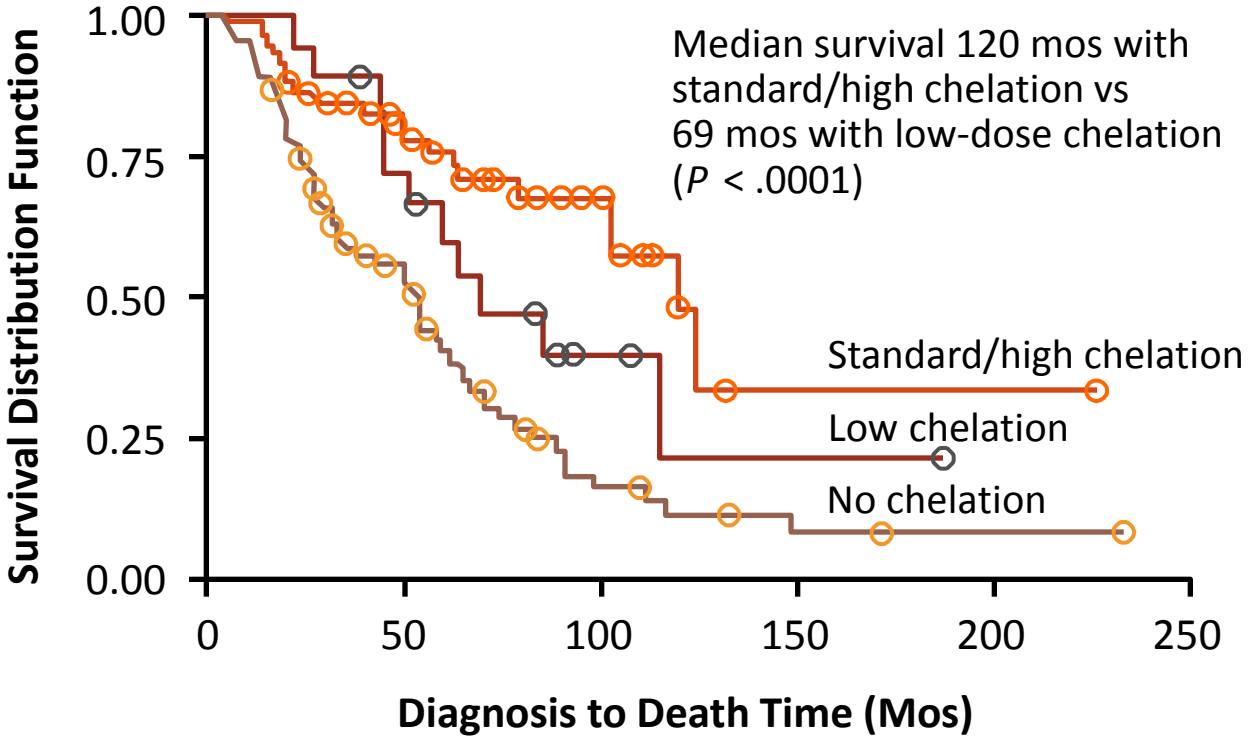
34

IRON CHELATION THERAPY

Does removing the excess iron improve anything?

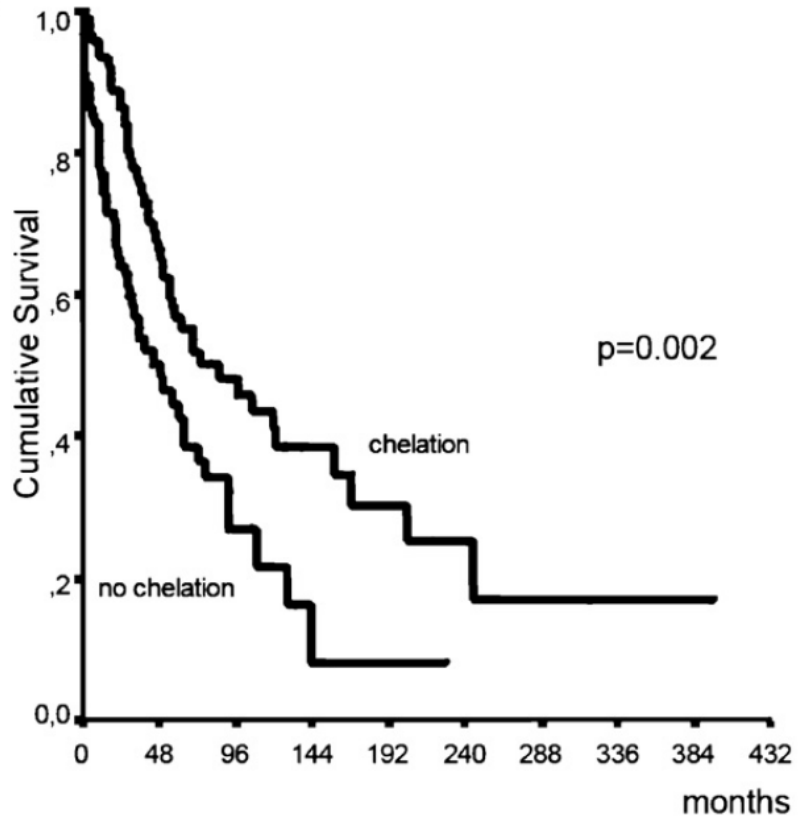
Nov 28, 2020 C. Hsia

IRON CHELATION THERAPY AND SURVIVAL IN MDS



List AF. *Cancer Control.* 2010;17:1-7.

IMPACT OF IRON CHELATION THERAPY ON OVERALL SURVIVAL



The difference in median survival (74 vs. 49 months, respectively; p = 0.002) supports the idea that iron chelation therapy is beneficial for MDS patients.

N=188

Neukirchen J, et al. Leuk Res. 2012 Aug;36(8):1067-1070.

EVIDENCE IN SUPPORT OF THE BENEFICIAL EFFECTS OF DEFEROXAMINE

N	Treatment	Assessment of efficacy	Findings
178 MDS (18 who received ICT)	DFO SC 0.5-3 g/day Over 12 h infusion 5 days /week	• Ferritin levels • Causes of death • Overall survival	• Median ferritin pre ICT was 4215μg/l and 2659μg/l post ICT - Ferritin increased in non ICT patients over time • IPSS score ($p < 0.008$) and ICT ($p = 0.02$) were the only factors independently predictive of OS • Median survival at 160 months for patients with low and Int-1 IPSS: - Not reached for those receiving ICT - 40 months for non ICT patients

ICT, iron chelation therapy
Leitch HA, et al. Blood 2006;108 [Abstract 249].

HEMATOLOGIC IMPROVEMENT IN MDS WITH DEFERASIROX

Reference	N	IPSS Risk	RBC Response	Neutrophil Response	Platelet Response	Median time to response
Cilloni D et al 2011*	57	Low/Int-1	45.6%	NR	NR	3 months
List A et al 2012*	173 52** 77***	Low/Int-1	15%	15%	22%	169 days (range, 84 to 382 days)
Gattermann N et al. 2010	247 50 100	Low/Int-1	21.5% (53/247)	22% (11/50)	13% (13/100)	113 days
Nolte F et al, 2012	50	Low/Int-1	11%	NR	NR	NR
Angelucci E et al. 2012	152	Low/Int-1	Transfusion independence in 12%	NR	NR	NR

*RBC, platelet, and neutrophil responses are assessed according to IWG 2006 criteria
**Met the neutrophil inclusion criteria
*** Met the platelet inclusion criteria

IPSS, International Prognostic Scoring System; RBC, red blood cell; NR, not reported; IWG, International Working Group.

1. Cilloni D, et al. ASH Annual Meeting 2011. Abstract 611; 2. List AF, et al. J Clin Oncol 2012; 30(17):2134-9; 3.Gattermann N, et al. ASH Annual Meeting 2010. Abstract 2912; 4. Nolte Fet al. Ann Hematol 2013; 92(2):191-198; 5. Angelucci E, et al. ASH Annual Meeting 2012. Abstract 425

CHARACTERISTICS OF CURRENTLY AVAILABLE IRON CHELATORS IN CANADA

Guidelines for the Clinical Care of Patients with Thalassemia in Canada
http://www.thalassemia.ca/wp-content/uploads/Thalassemia-Guidelines_LR.pdf

CHARACTERISTICS OF CURRENTLY AVAILABLE IRON CHELATORS IN CANADA

Characteristics	Deferoxamine	Deferiprone	Deferasirox
Route of administration	Subcutaneous or intravenous	Oral	Oral
Plasma half-life	Short (20 min)	Moderate (2 hrs)	Long (8-16 hrs)
Primary route of iron excretion	Urine and stool	Urine	Stool
Recommended dosage (mg/kg/day)	30-60	75 -100	10 -40
Delivery	s.c.or i.v. (8-12 hours) 5-7 days/week	Oral, 3 times daily	Oral, once daily
Charge of iron (III) complex (hydrophilic or lipophilic)	Charged Hydrophilic	Uncharged Lipophilic	Uncharged Lipophilic

Guidelines for the Clinical Care of Patients with Thalassemia in Canada
http://www.thalassemia.ca/wp-content/uploads/Thalassemia-Guidelines_LR.pdf

CANADIAN PANEL RECOMMENDATIONS: PATIENT SELECTION FOR IRON CHELATION THERAPY

- Iron chelation should be considered for transfusion-dependent MDS patients with a good prognosis (Low or Int-1 IPSS score or WHO classification of RA,RARS, or 5q-syndrome) as well as a higher IPSS score (Int-2 or High) who have:
  - Serum ferritin>1000 μg/L, or
  - Who are candidates for allogeneic stem cell transplantation, or
  - Have a life expectancy >1 year
- Iron chelation should be initiated when transfusion-dependent patients:
  - Have evidence of iron-related organ damage, or
  - Have serum ferritin >1000 μg/L and fasting transferrin saturation >0.5, irrespective of the number of units of blood transfused

Wells RA, et al. *Leuk Res*. 2008;32(9):1338-1353.

OTHER RECOMMENDATIONS FOR MANAGEMENT OF IRON OVERLOAD IN MDS PATIENTS

Characteristics	NCCN	MDS Foundation
Transfusion status	Received > 20 RBC transfusions; Continuing transfusions	Transfusion dependent, requiring 2 U/mo for >1 y
Serum ferritin concentration	> 2500 μg/L	> 1000 μg/L
MDS risk category	IPSS: low or intermediate-1	IPSS: low or intermediate-1; WHO: RA, RARS, and 5q-
Patient profile	Candidate for allograft	Candidate for allograft; need to preserve organ function; Life expectancy >1 y without comorbidities limiting progress

Gattermann, N. *Int J Hematol*. 2008;88(1):24-29.
Bennett JM, et al. Am J Hematol. 2008;83(11): 858-861.

CANADIAN PANEL RECOMMENDATIONS: CHOICE OF CHELATING AGENT*

- Once the decision has been made to initiate iron chelation therapy, either DFO or DSX may be used
  - DFO 20–50 mg/kg/day by subcutaneous or intravenous infusion over 12–15 h or by BID SC bolus injections 5 days/week
  - DSX 20–30 mg/kg PO QD
- Baseline investigations prior to the initiation of chelation therapy
  - Ophthalmological examination (slit lamp, retinal and corneal assessments)
  - Audiometry
  - Complete blood count
  - Creatinine (for DSX)

*Recommendations were written before deferiprone was approved in Canada
DFO, Deferoxamine; DFX, Deferasirox
Wells RA, et al. *Leuk Res*. 2008;32(9):1338-1353.

EAP REQUIREMENTS IN ONTARIO

DRUG NAME	BRANDS REIMBURSED	DOSAGE FORM/ STRENGTH	REIMBURSEMENT CRITERIA	STANDARD APPROVAL DURATION
Deferasirox	Exjade	125 mg, 250 mg, 500 mg tablet	**For the treatment of chronic iron overload in transfusion-dependent anemia in those with low-risk myelodysplastic syndrome (MDS) or other rare anemias (e.g. Diamond Blackfan)** in patients who have a contraindication or severe intolerance to deferoxamine. Contraindications may include one or more of the following: • known or suspected hypersensitivity to deferoxamine • recurrent injection or infusion-site reactions (e.g., cellulitis) • concomitant bleeding disorder • immunocomprimised patients with a documented risk of significant infections with parenteral administration (e.g. neutropenia) **Renewals** will be considered on a case-by-case basis. Physicians must provide adequate information to support the request for renewal.	Initial: 1 year Renewal: 5 years

EAP Reimbursement Criteria Updated April 30, 2014

CANADIAN PANEL RECOMMENDATIONS: ROUTINE FOLLOW-UP OF AND DOSE ADJUSTMENTS

Routine follow-up

- Clinic visit once monthly for 3 months, then quarterly (once every 3 months)
- Ferritin, TSH/T3/T4, LFTs, creatinine, glucose q3monthly (CBC and creatinine weekly for four weeks after initiation of DSX therapy and after any dose increase)
- Urinalysis (for proteinuria) monthly for DSX
- Annual audiometry and ophthalmological assessments
- 2D echo, if abnormal at baseline or if clinically indicated

Dosage adjustments

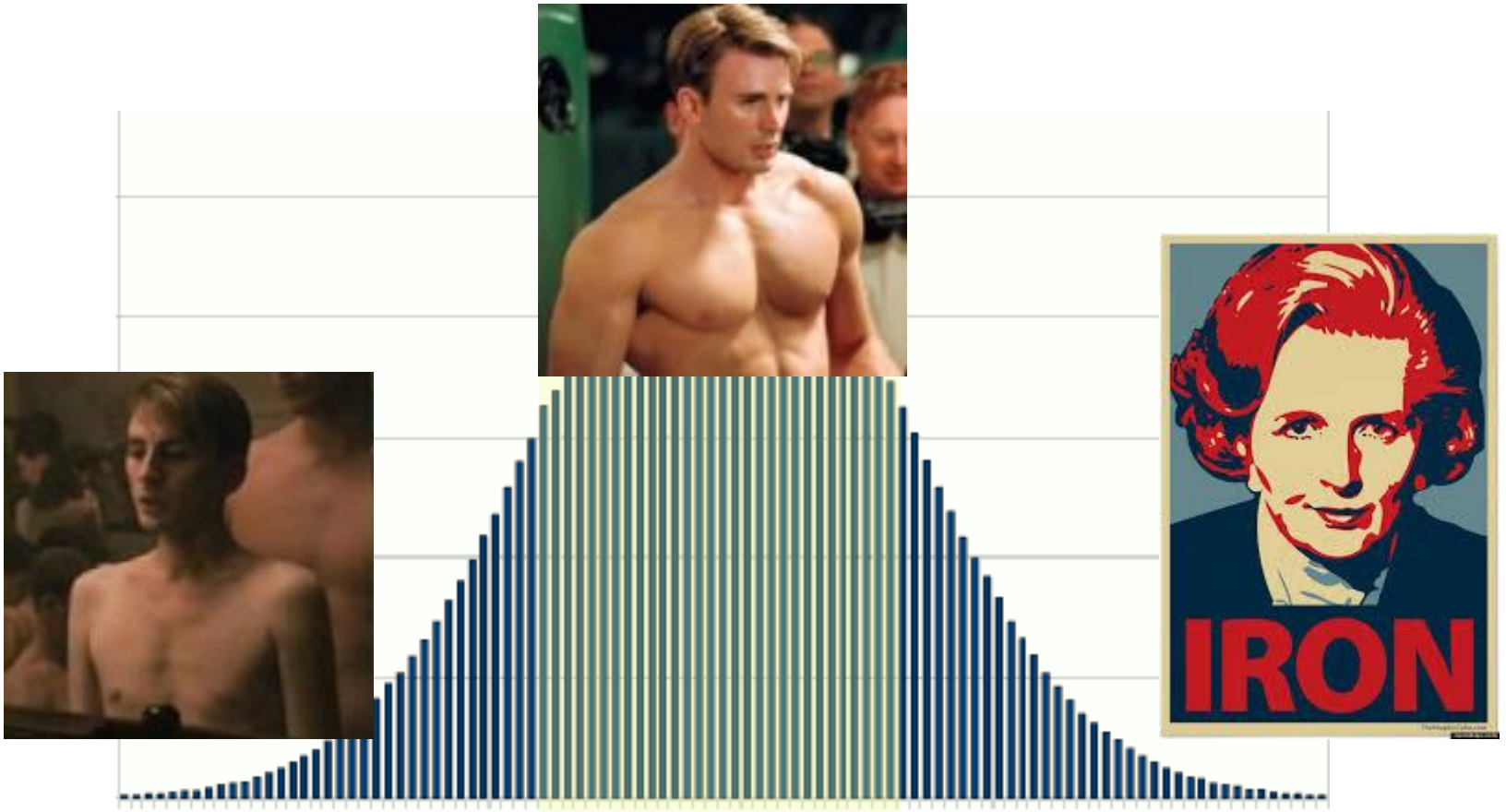
- Reduce dose of iron chelation therapy when ferritin falls below 2000 μg/L
- Discontinue iron chelation therapy when ferritin <1000 μg/L
- For DSX, follow product monograph if creatinine is elevated

Wells RA, et al. *Leuk Res*. 2008;32(9):1338-1353.

SUMMARY

- Iron is essential in the production and function of hemoglobin and red blood cells.
- Too little iron (iron deficiency anemia) and too much iron (iron overload) can be detrimental
- Number of RBC transfusions and iron overload are important yet often neglected issues in MDS management that appear to be negative predictors of survival
- Iron chelation therapy should be considered in the management of MDS patients with iron overload due to frequent transfusions

SO WHERE DO YOU WANT TO BE?



Bone marrow factory - The future
Any Questions?

REFERENCES

- ASH Education Book 2005 – 2015
- World Health Organization Classification of Tumours. Pathology & Genetics: Tumours of Haematopoietic and Lymphoid Tissues. Edited by Elaine S. Jaffe, Nacy Lee Harris, Harald Stein, James W. Vardiman. IARC Press Lyon 2001.
- Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. British Journal of Haematology. 1982; 51:189-199.
- Harris NL, Jaffe ES, Diebold J, et al. World Health Organization Classification of Neoplastic Diseases of the hematopoietic and lymphoid tissues: report of the clinical advisory committee meeting – Airlie House, Virginia, November 1997. J Clin Oncol. 1999;17:3835-3849.
- Greenberg P, Cox C, LeBeau MM, et al. International Scoring System for evaluating prognosis in myelodysplastic syndromes. Blood. 1997;89:2079-2088.
- Greenberg PL, Sun Z, Miller KB, Bennett JM, Tallman MS, Dewald G, Paietta E, van der Jagt R, Houston J, Thomas ML, Cella D, Rowe JM. Treatment of myelodysplastic syndrome patients with erythropoietin with or without granulocyte colony-stimulating factor: results of a prospective randomized phase 3 trial by the Eastern Cooperative Oncology Group (E1996). Blood. 2009 Sep 17;114(12):2393-400. PMID: 19564636
- Steensma DP and Bennett JM. The Myelodysplastic Syndromes: Diagnosis and Treatment. Mayo Clin Proc. 2006;81(1):104-130.
- Komrokji RS and Bennett JM. Evolving classifications of the myelodysplastic syndromes. Current Opinion in Hematology. 2007;14:98-105.
- Hellström-Lindberg E, Ahlgren T, Beguin Y, et al. Treatment of anemia in myelodysplastic syndromes with granulocyte colony-stimulating factor plus erythropoietin: results from a randomized phase II study and long-term follow-up of 71 patients. Blood. 1998 Jul 1;92(1):68-75.
- Malcovati L. Prognostic Factors and Life Expectancy in Myelodysplastic Syndromes Classified According to WHO Criteria: A Basis for Clinical Decision Making. J Clin Oncol 2005;23:7594-7603.
- Garcia-Manero G. Standard-of-care Approaches for Myelodysplastic Syndromes. JCO 2009 Education Book pp 408-412.
- Garcia-Manero G. Demethylating agents in myeloid malignancies. Current Opinion in Oncology. 2008;20:705-710.
- Fenaux P, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomized, open-label, phase III study. Lancet Oncol 2009;10:223-32.
- Silverman LR, et al. Randomized Controlled Trial of Azacitidine in patients with Myelodysplastic Syndrome: A Study of the Cancer and Leukemia Group B. JCO 20:2429-2440.
- Stresemann C and Lyko F. Modes of action of the DNA methyltransferase inhibitors azacytidine and decitabine. Int J Cancer 2008;123:8-13.
- Tefferi A, Vardiman JW. Myelodysplastic syndromes. N Engl J Med. 2009 Nov 5;361(19):1872-85. PMID: 19890130

ACKNOWLEDGEMENTS

- Select slides taken from Dr. Richard Wells' presentation – The Silent Disease: Management of Iron Overload in Daily Practice

APPENDICES

ASSESSMENT OF IRON OVERLOAD AND COMMON ADVERSE EVENTS OF

Observation	Frequency	IOL assessment	AE monitoring
Iron intake rate	Each transfusion	✓	
Chelation dose and frequency	3 monthly	✓	✓
Renal function[a]	As frequently as required		✓
Liver function	3 monthly	✓	✓
Sequential serum ferritin, transferrin saturation[b]	3 monthly	✓	
GTT, thyroid, calcium metabolism (BMD)[c]	Yearly in adults	✓	
Liver iron (T2* MRI)[d]	At baseline, where feasible; and, subsequently, as clinically indicated		
Cardiac function (echo, MRI, ECG)	At baseline, then as clinically indicated	✓	
Cardiac iron (T2* MRI)	For patients receiving > 50 units RBC prior to ICT, or with CHF or arrythmias	✓	
Slit lamp examination, audiometry[e]	Yearly		✓

[a]Creatinine should be measured at least every two weeks with each dose increase until stable. [b]Transferrin saturation > 80% may indicate the presence
of oxidative stress. [c]Based on early/suggestive data in transfusion-dependent hemoglobinopathies. [d]Hepatic IOL is underestimated in up to 25% of patients. [e]Ocular & audiological side effects have been reported at low ferritin levels.

Leitch HA. How I treat iron overload in MDS and why. Canadian Perspectives in Clinical Hematology