Iron Overload in Bone Marrow Failure

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Iron Overload in Bone Marrow Failure: Questions and Answers

- How is iron regulated in the body?
- How does iron overload occur?
- Why is too much iron bad?
- How can we tell if there is too much iron?
- How do we get rid of excess iron?
- What are the guidelines for chelation therapy in MDS?
- Why don't all physicians offer chelation?
- Future directions

Case presentation: M. S.

- June 2007: 77 yr old female
- 1 yr Hx anemia and macrocytosis
- Transfused intermittently (outside institution)
- 4 mos. Hx SOB, fatigue, unable to do ADL
- Refused to undergo marrow asp/bx, agreed to transfuse if Hb < 90 due to CAD

Case presentation cont'd

- October 2007: FU visit: agreed to marrow biopsy (apply for ESA), prescribed Exjade (ferritin 1319)

Case presentation cont'd

DOB: 29APR02 SEX: FEMALE
DOCTOR: FORGIE MA
ENCOUNTER NO. 48856221

ADMITTED: 2007/10/09 DISCH: 2007/10/19 AC PAGE: 2

DIAGNOSIS:
Bone marrow aspirate:
- Myelodysplastic syndrome.
- Refractory anemia with ringed sideroblasts (RARS).

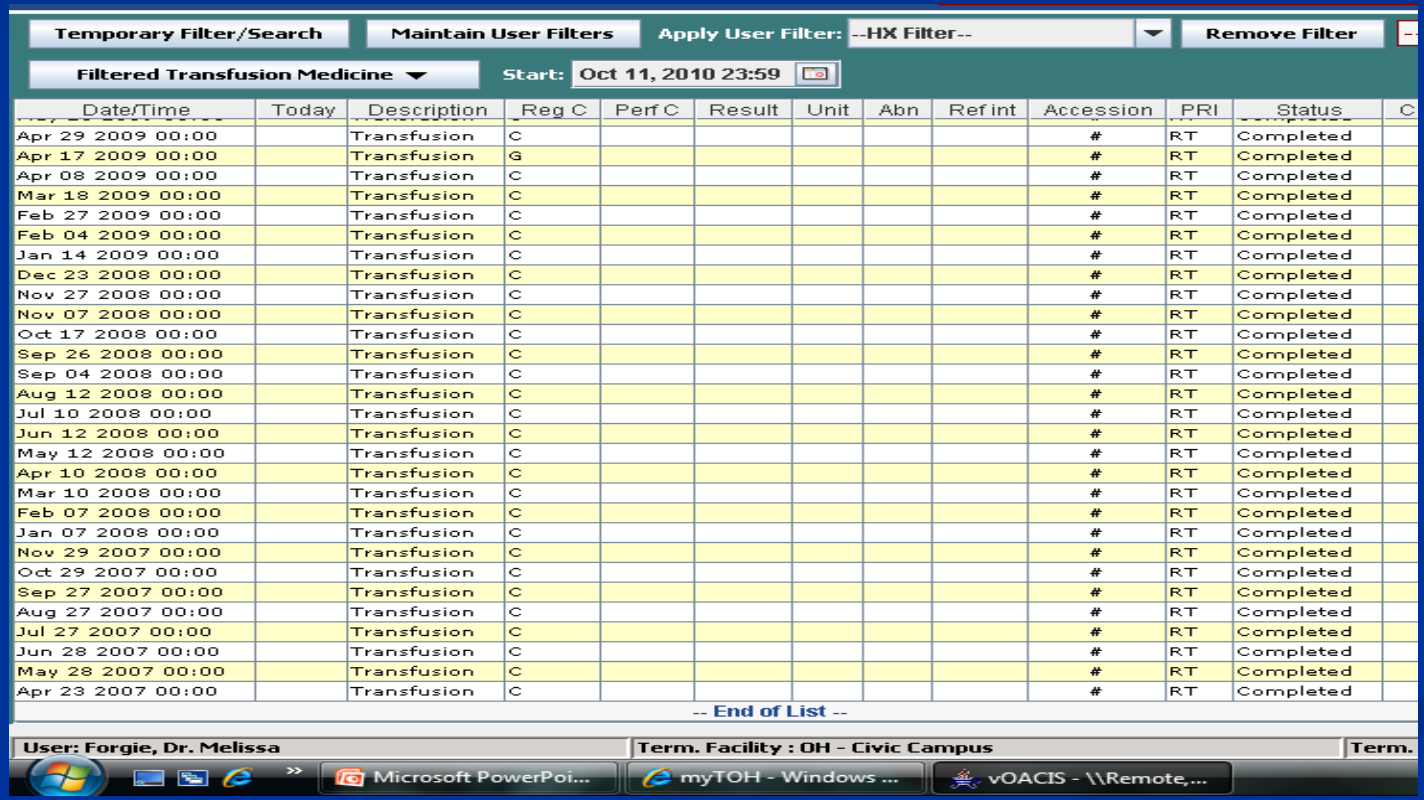
JB /cae
Verified by: J. Bormanis, M.D., FRCPC (Electronic signature)
Verified date: 07/10/15

Cytogenetics normal

Comment

There are no comments associated with this test

Case presentation cont'd



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Filtered Transfusion Medicine | Start: Oct 11, 2010 23:59

Date/Time	Today	Description	Reg C	Perf C	Result	Unit	Abn	Ref int	Accession	PRI	Status	C
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Apr 17 2009 00:00		Transfusion	G						#	RT	Completed	
Apr 08 2009 00:00		Transfusion	C						#	RT	Completed	
Mar 18 2009 00:00		Transfusion	C						#	RT	Completed	
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User: Forgie, Dr. Melissa | Term. Facility : OH - Civic Campus | Term.

Microsoft PowerPoi... | myTOH - Windows ... | vOACIS - \\Remote,...

Case presentation cont'd

- Feb. 2010: severe CHF, admits to never taking Exjade consistently (explains erratic ferritin, dose increases limited by kidney function)
- T2* cardiac MRI signal 7.2
- Prescribed DFO with transfusions and daily sc infusion through homecare

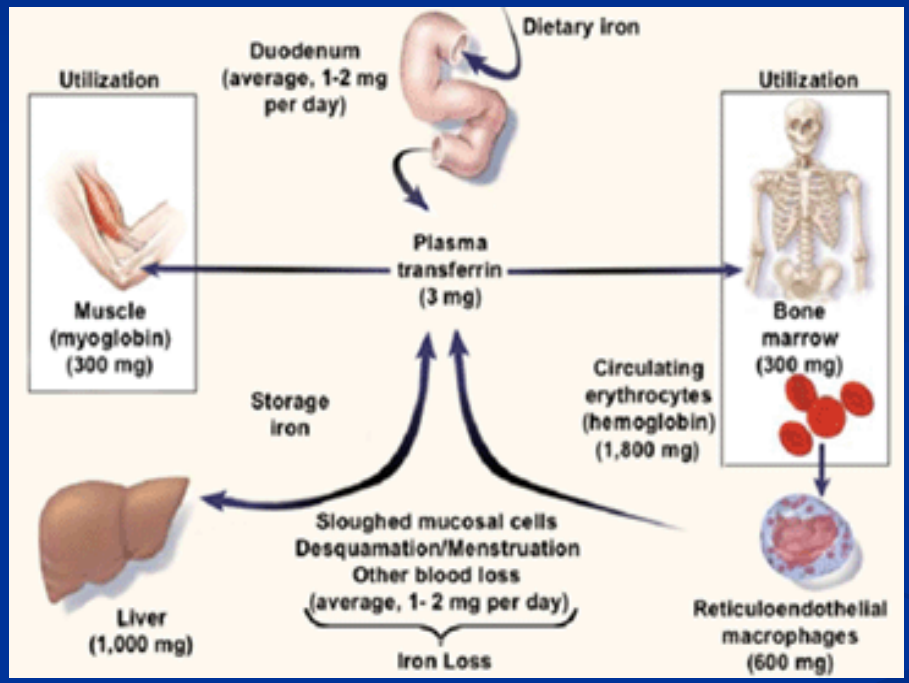
Case presentation cont'd: clinic note July 2010

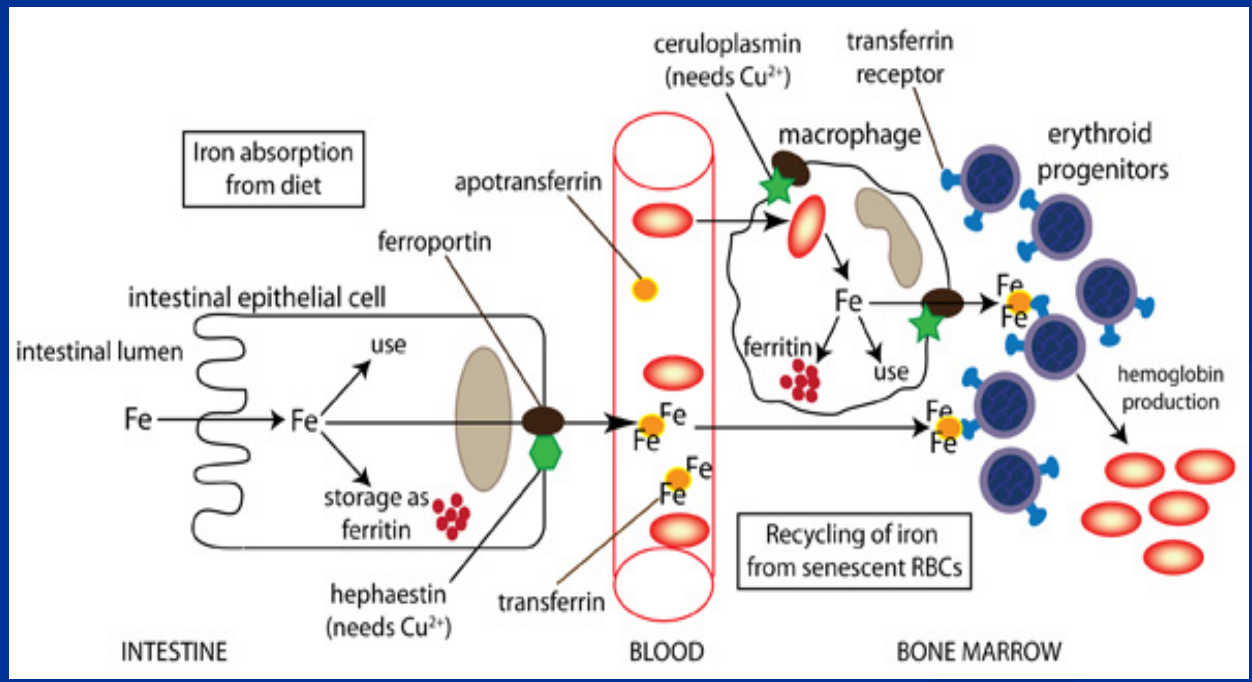
advanced myelodysplasia, which has been complicated by transfusional associated iron overload. She developed congestive heart failure and was placed on home care for subcutaneous Deferoxamine infusions. She has had significant improvement in her cardiac symptomatology and her iron indices have improved significantly, with her Ferritin decreasing from 4000 to currently 1900. She is only being transfused approximately every two to three months and was transfusion free between February and June. Her most recent blood work shows hemoglobin of 90, white cell count of 11.4, platelet count of 192, a neutrophil

Ferritin from 4995 to 1900

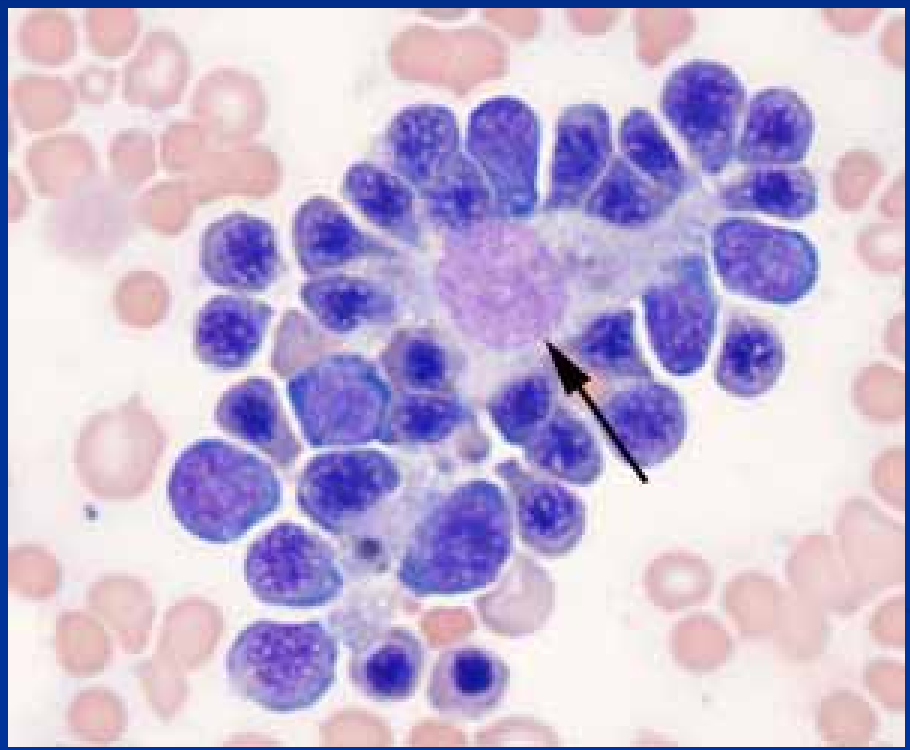
How is iron regulated in the body?

Iron metabolism: homeostasis

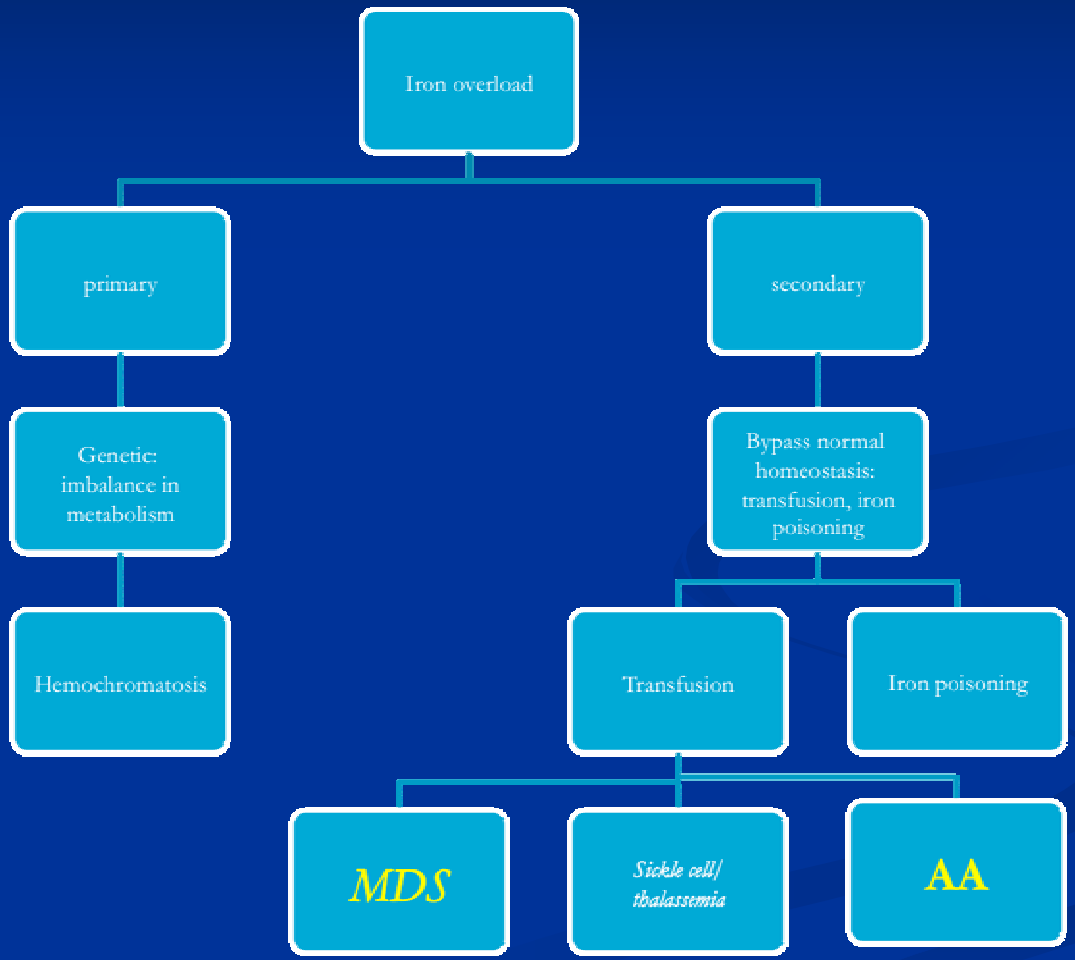



ceruloplasmin
(needs Cu2+)
transferrin
receptor
macrophage
erythroid
progenitors
Iron absorption
from diet
apotransferrin
ferroportin
intestinal epithelial cell
intestinal lumen
use
Fe
Fe
Fe
ferritin
use
Fe
Fe
hemoglobin
production
storage as
ferritin
Fe
Fe
Fe
Fe
Recycling of iron
from senescent RBCs
hephaestin
(needs Cu2+)
transferrin
INTESTINE
BLOOD
BONE MARROW

Iron uptake from macrophages for red blood cell synthesis



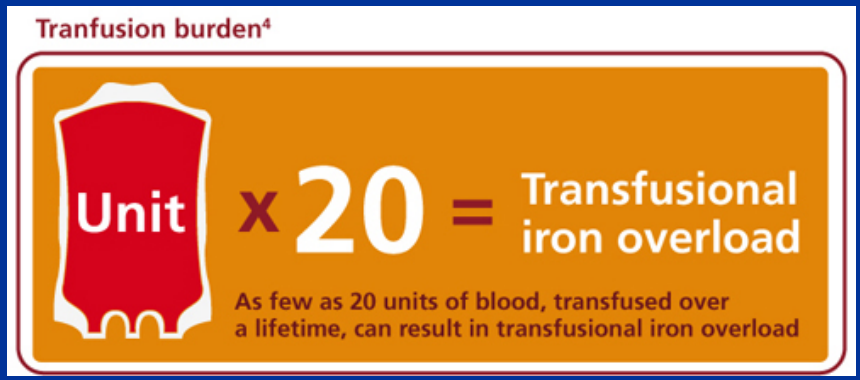
How does iron overload occur?

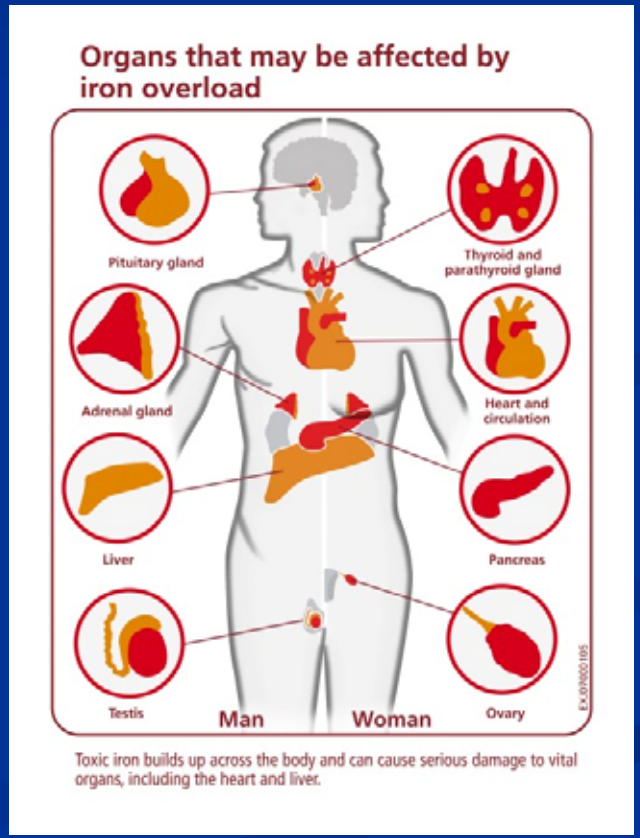


How does iron overload occur?

- Each unit of blood contains approximately 250 mg of iron
- That means an excess of 500 mg of iron with a 2 unit transfusion
- Recall the body can excrete about 1-2 mg per day; each unit is 10X amount the body can excrete
- Recall the body is good at storing iron

Tranfusion burden[4]

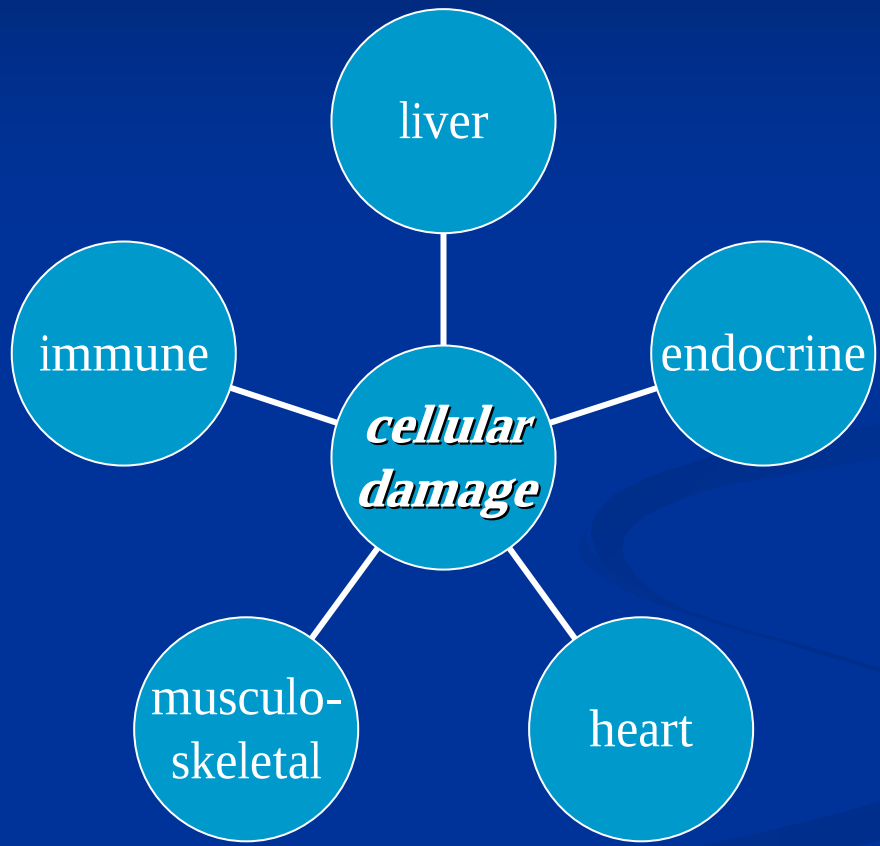




Why is too much iron bad?

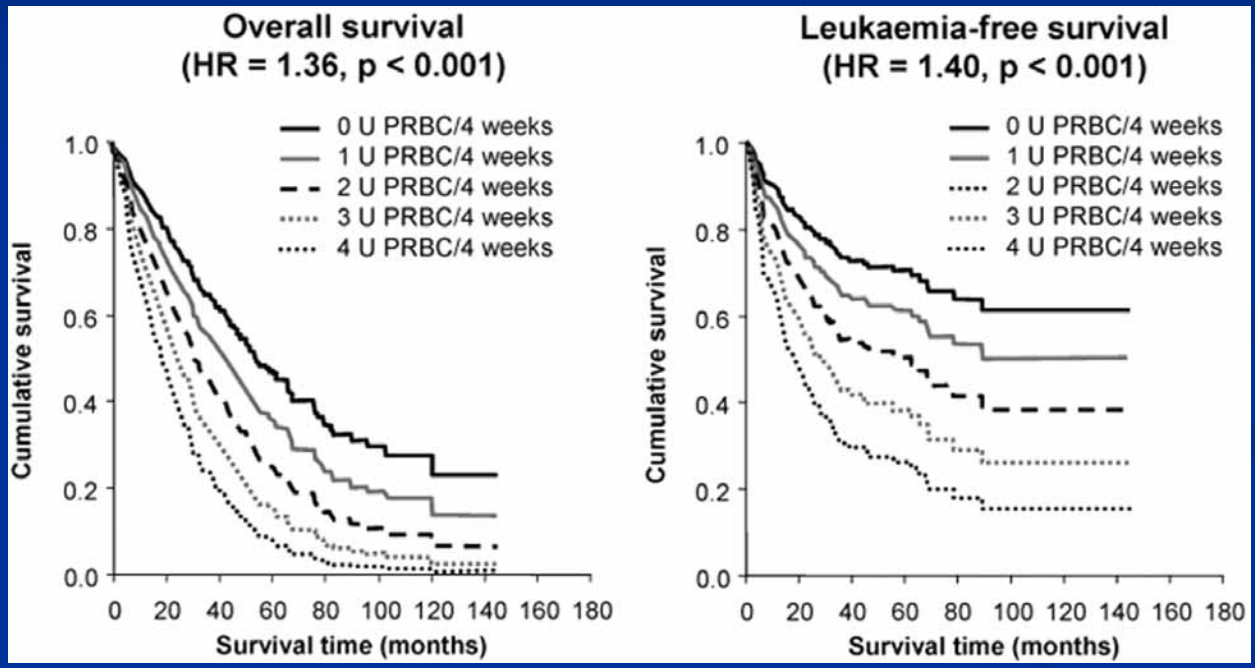
- In addition to accumulation in organs which causes organ dysfunction, when transferrin saturation exceeds 75%, non-transferrin bound iron (NTBI) appears and leads to formation of labile plasma iron (LPI) and reactive oxygen species (ROS)
- LPI and ROS are directly toxic to tissues

Consequences of iron overload



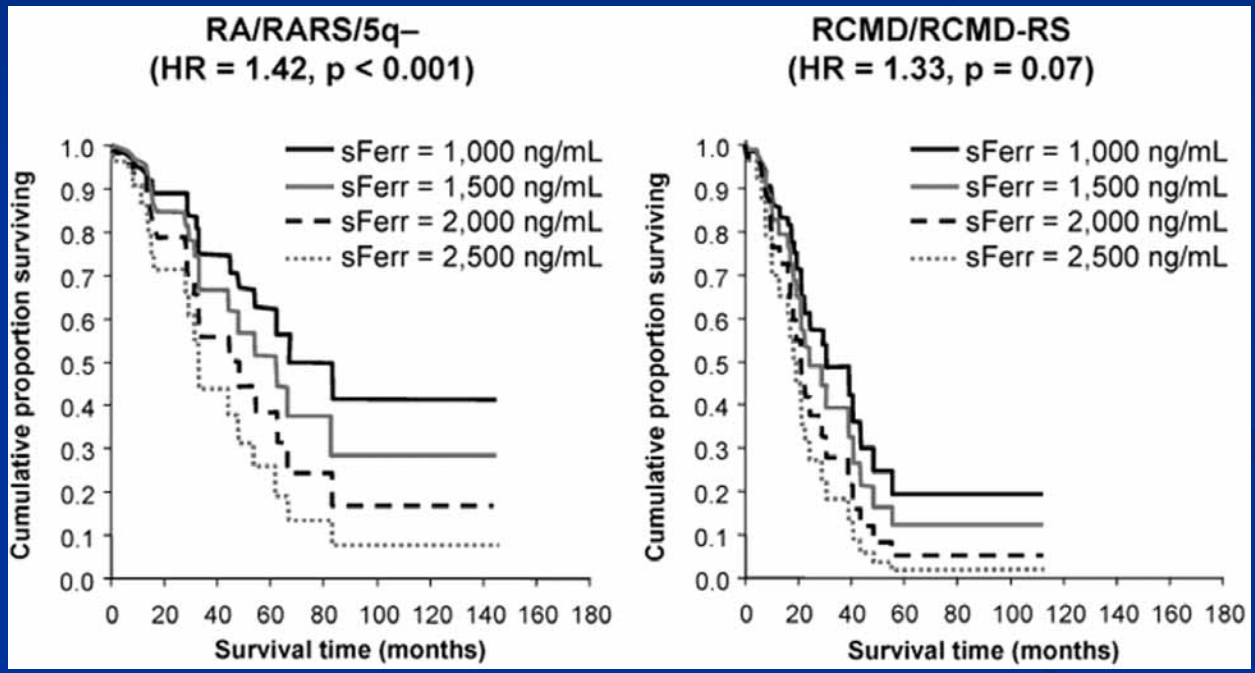
Okay, so it looks like too much iron may be a bad thing but show me the evidence...

Figure 1. Survival of patients with myelodysplastic syndrome (MDS) according to the severity of transfusion requirement; overall survival is shown in the left panel and leukemia-free survival on the right



Leitch, H. A. et al. Hematology 2009;2009:664-672

Figure 2. Overall survival of transfusion-dependent patients with myelodysplastic syndrome (MDS) according to ferritin level



Leitch, H. A. et al. Hematology 2009;2009:664-672

How can we tell if there is too much iron?

- Start screening after 20 units
- Typically done with simple blood tests at first: serum transferrin saturation (> 45%), serum ferritin (>1000 ng/mL)

Pitfalls of blood tests

- Depending on cutoff for transferrin saturation
- Ferritin elevated with inflammation, excess alcohol, other liver diseases
- Discordance between ferritin and iron overload

blood
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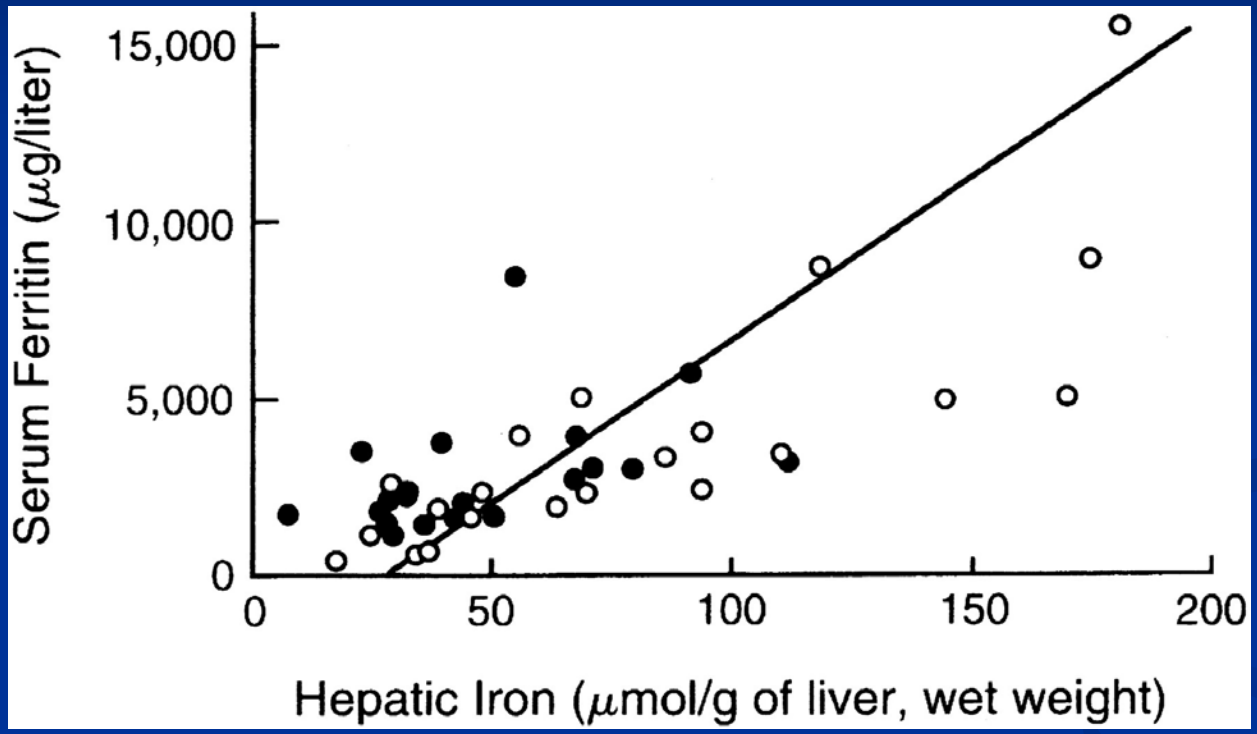
Figure 2.



Olivieri, N. F. et al. Blood 1997;89:739-761

Screening and diagnosis of iron overload

- Blood tests
- Direct measurement: liver (LIC), cardiac biopsy
- Imaging: MRI, T2*MRI, SQUID, echo, radionuclide ventriculography

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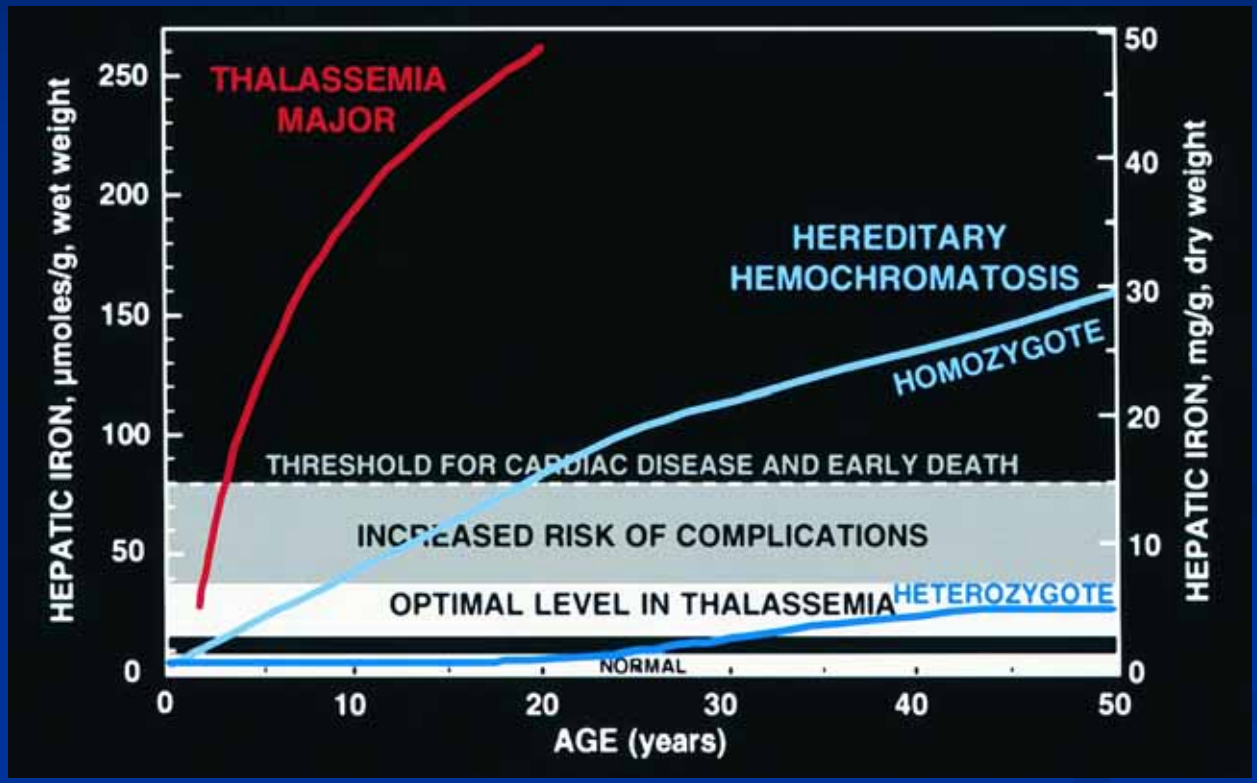
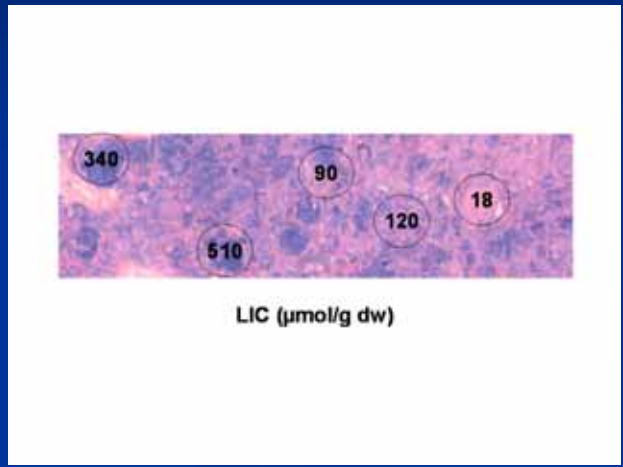
Figure 6.

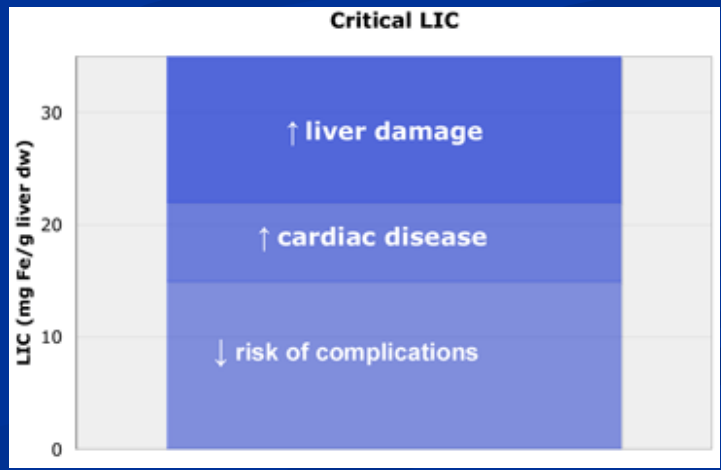


Olivieri, N. F. et al. Blood 1997;89:739-761

Liver and cardiac biopsy

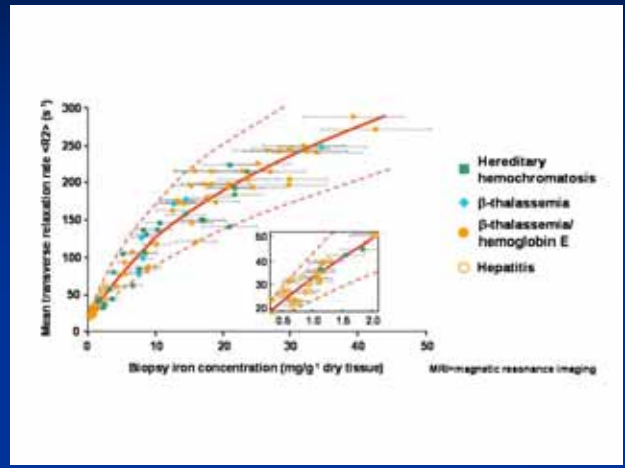
- LIC: gold standard
- LIC > 15: high risk of cardiac complications and death
- LIC > 19: cirrhosis, fibrosis
- LIC used to guide chelation therapy and dosing
- Invasive, acceptable in BTM but not MDS (co-morbidities, cytopenias)
- Sampling errors
- Variability between labs
- Cardiac more invasive



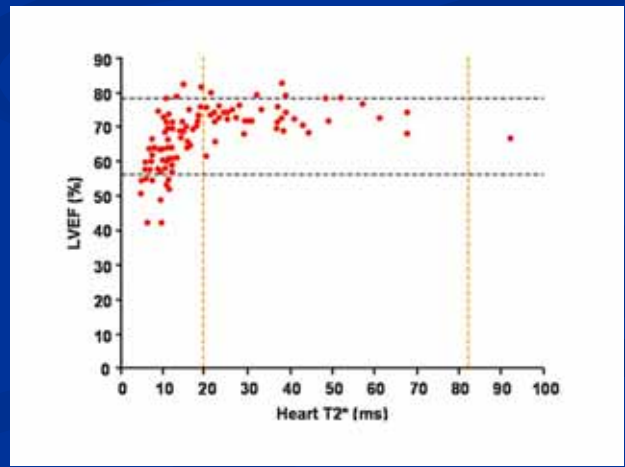


Imaging

- R2 (T2*)MRI liver: non-invasive, evaluates entire organ

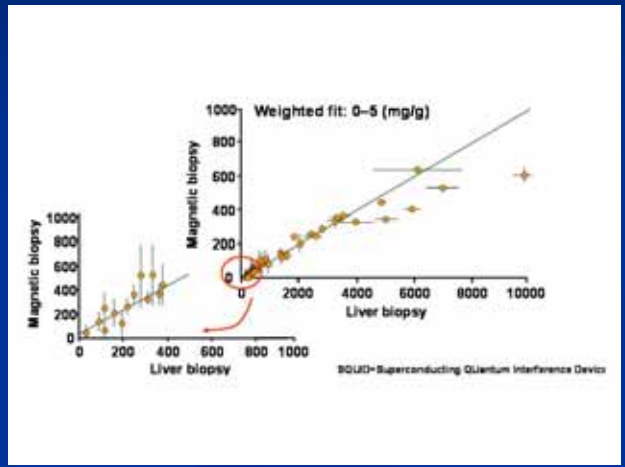


- T2* MRI: standard for cardiac iron



Superconducting Quantum Interference Device (SQUID)

- Low power magnetic field
- Measures iron interference with the field
- Sensor requires cryogenic environment
- Only 5 world-wide: none in Canada
- Piga et al., Blood, 2005 (abs)



T2* cardiac MRI and R2 liver MRI General Campus

Ferriscan®

- Wider range of LIC than conventional T2* MRI
- May not be necessary for shorter term chelation but will allow for more precise titration of chelation
- Available at CHEO soon

Echo and radionuclide scanning

- Non invasive
- Widely available
- Diastolic dysfunction prognostic value
- Abnormalities develop late: T2*MRI earlier detection
- Measurement of LVEF superior with radionuclide angiography

Liver versus heart: predictors?

- No correlation
- Cardiac iron clearing 6X more slowly
- Cardiac dysfunction with low liver Fe
- LIC > 15 predictive of cardiac disease, early death (Anderson, Eur Heart J., 2001)
- Lower rates of cardiac iron deposition in MDS than with BTM (higher transfusion burden needed; 75-100 units)

blood
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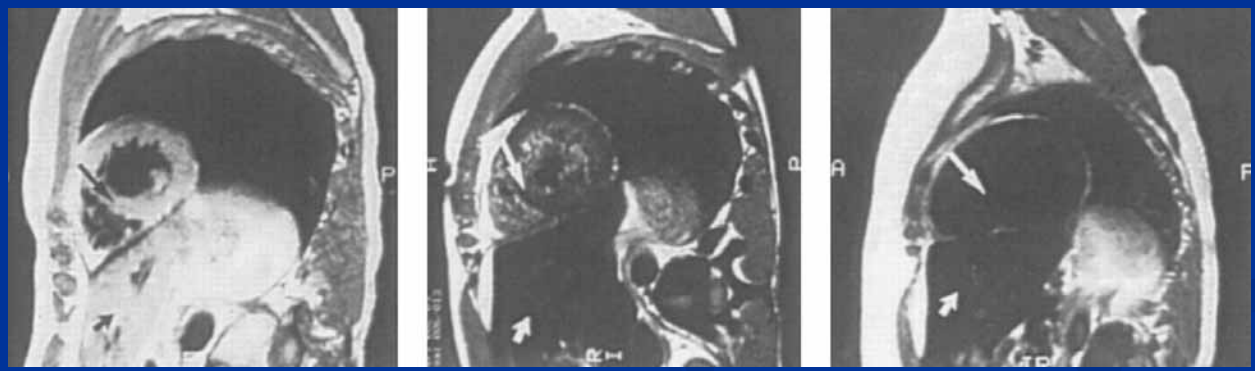
Figure 4.



Olivieri, N. F. et al. Blood 1997;89:739-761

Comparison of methods for assessment of iron overload

Method	Advantages	Disadvantages
Serum ferritin	Non-invasive, inexpensive, rapid, Longitudinal FU	Indirect, Poor correlation with gold standard, Varies by etiology
Liver biopsy: LIC	Reference standard, direct measurement, correlates with morbidity and mortality	Invasive, painful, requires skilled personnel, may not be representative, of entire organ, difficult to FU, risky in some MDS patients
MRI	Non-invasive, whole organ, more available than LIC, longitudinal FU, T2* gold standard for cardiac imaging, Ferriscan®	Indirect measure, sedation for children or those with claustrophobia, specialized software
SQUID	Non invasive, linear correlation with LIC	Limited availability, costly, complex, may underestimate LIC

Measurement of iron: liver versus heart

Liver

- LIC
- MRI R2 (T2*)
- SQUID
- Ferriscan®

Heart

- LVEF
- MRI T2*

Canadian Consensus Guidelines for chelation in MDS

- Ferritin > 1000
- transferrin saturation > 50%
- 2 units RBC per month > 1 yr
- No response to primary treatment or ineligible
- Imminent transplant
- Survival > 1 yr
- Compromised organ function

Who should be offered chelation?

- Low to int 1 MDS
- Pre and post BMT
- Consider in higher risk MDS
- No clear data for AA; extrapolate from MDS data

Treatment of iron overload

uOttawa

Treatment of iron overload: based on mechanism of iron distribution

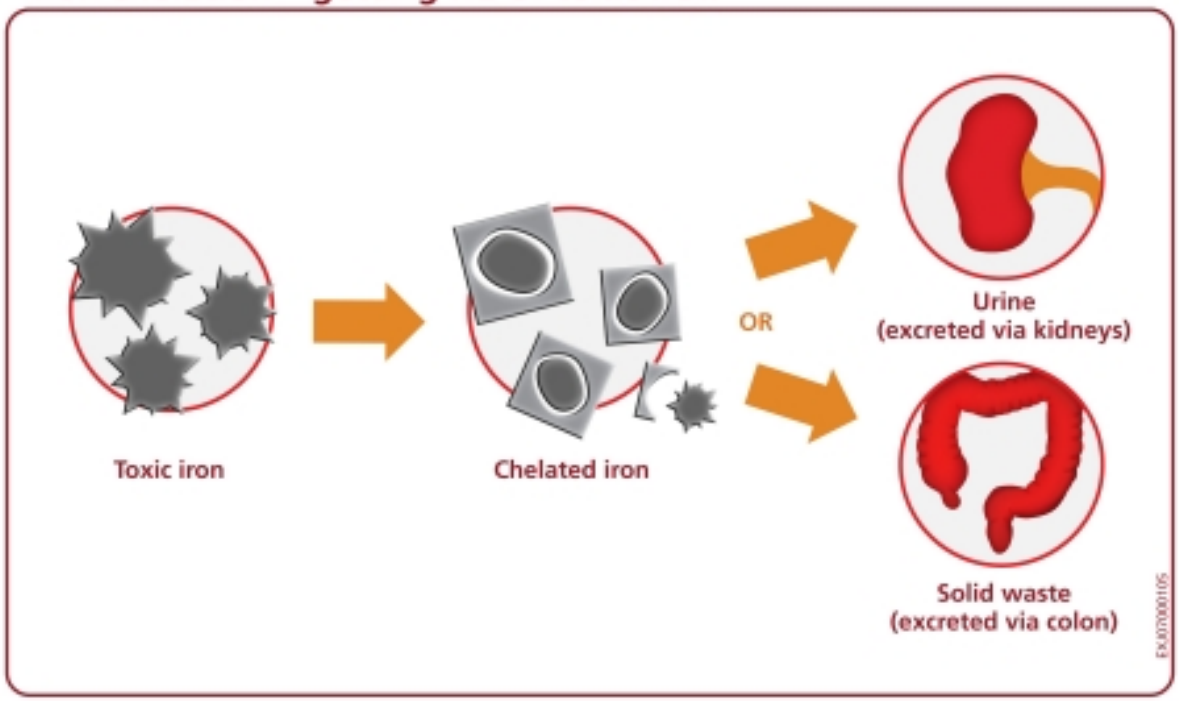
Hemochromatosis:

- gradual
- more in parenchyma, less in macrophages
- phlebotomy
- intermittent

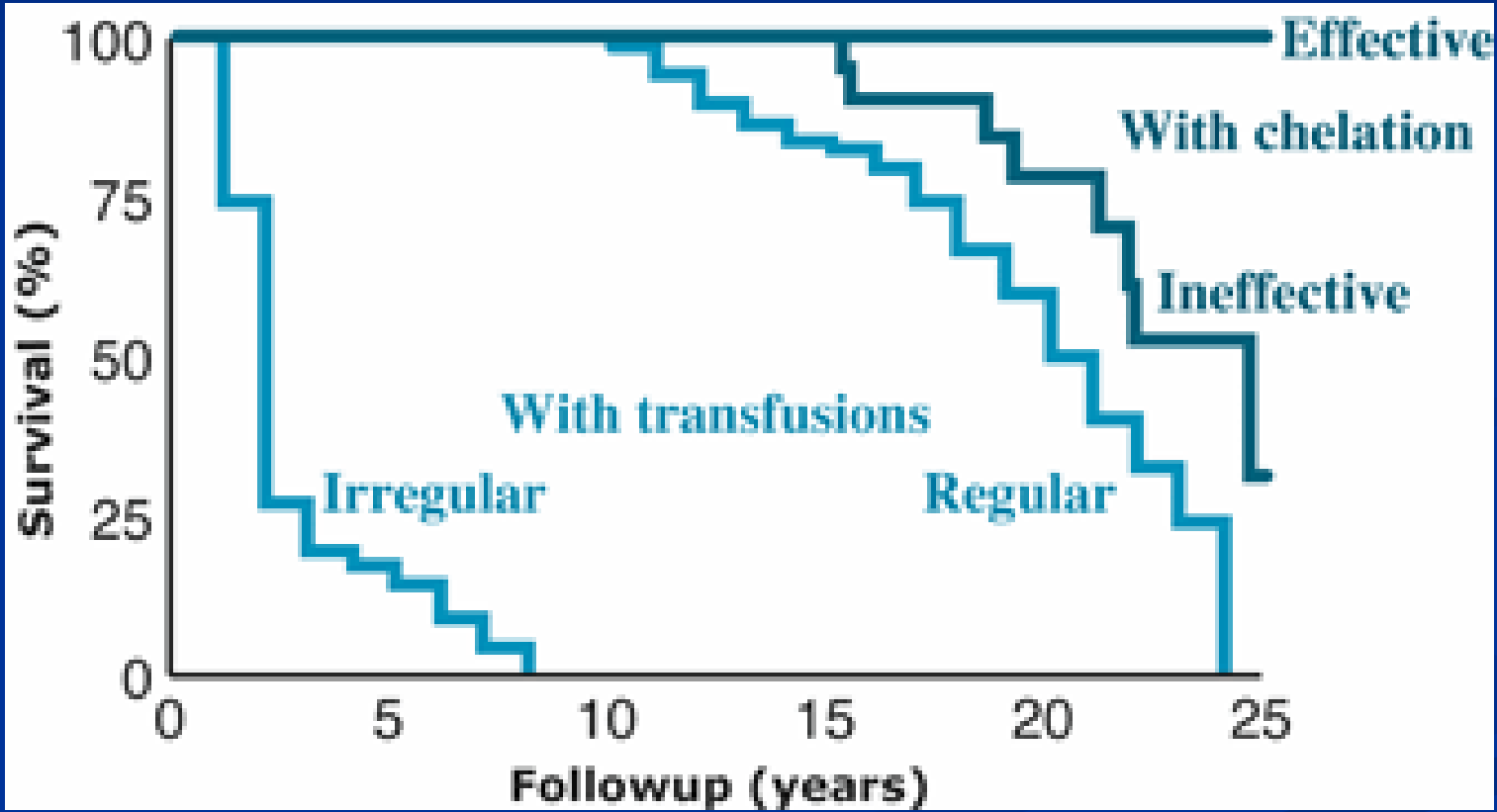
Transfusional iron overload:

- anemia has already reduced RBC iron pool
- sudden
- increased NTBI
- morbidity greater than primary iron overload
- chelation
- constant

How does chelation work?



Chelation therapy



What do we hope to achieve with chelation?

- Improve survival
- Preserve heart function
- Preserve liver function
- Improve hematopoeisis (QOL)
- Preserve function of other organs: endocrine

Comparison of iron chelators

Characteristics	***Deferoxamine (Desferal)***	***Deferasirox (Exjade)***
Route administration	sc or iv	oral
Half-life	20 min.	8-16 hrs
Routes iron excretion	Urine, stool	stool
Monitoring	Eye and ENT q 1 yr, ferritin, assess liver Fe q 1 yr, assess cardiac Fe q 1 yr	Creatinine, urine, ALT monthly, ferritin, assess liver Fe q 1 yr assess cardiac Fe q 1 yr
Advantages	Long term experience, effective in maintaining near normal Fe, reverses cardiac disease with intensive Rx,	Orally active, OD, equivalency to deferoxamine at higher doses, trials in several disorders
Side effects	Eye, ENT, local skin reactions, growth	Eye, ENT, GI, rash, HA, ↑LFT, ↑Cr, cytopenias
Disadvantages	Parenteral, eye, ear, bone toxicity, poor compliance, skin reactions	Monitor renal function, may not achieve negative iron balance in all patients

Does chelation work in MDS and AA

- Well established efficacy in hereditary anemias
- Some evidence that transfusion dependence and iron overload confer worse prognosis in MDS (recall slide 25; Leitch et al.)
- Chelation may actually improve survival
- All retrospective data, small numbers

Show me the evidence...

- Does chelation work in MDS?

  EPIC trial: prospective, 341 MDS patients, 116 AA patients (1744 patients total); YES
- Okay, so chelation lowers ferritin but does chelation improve survival?

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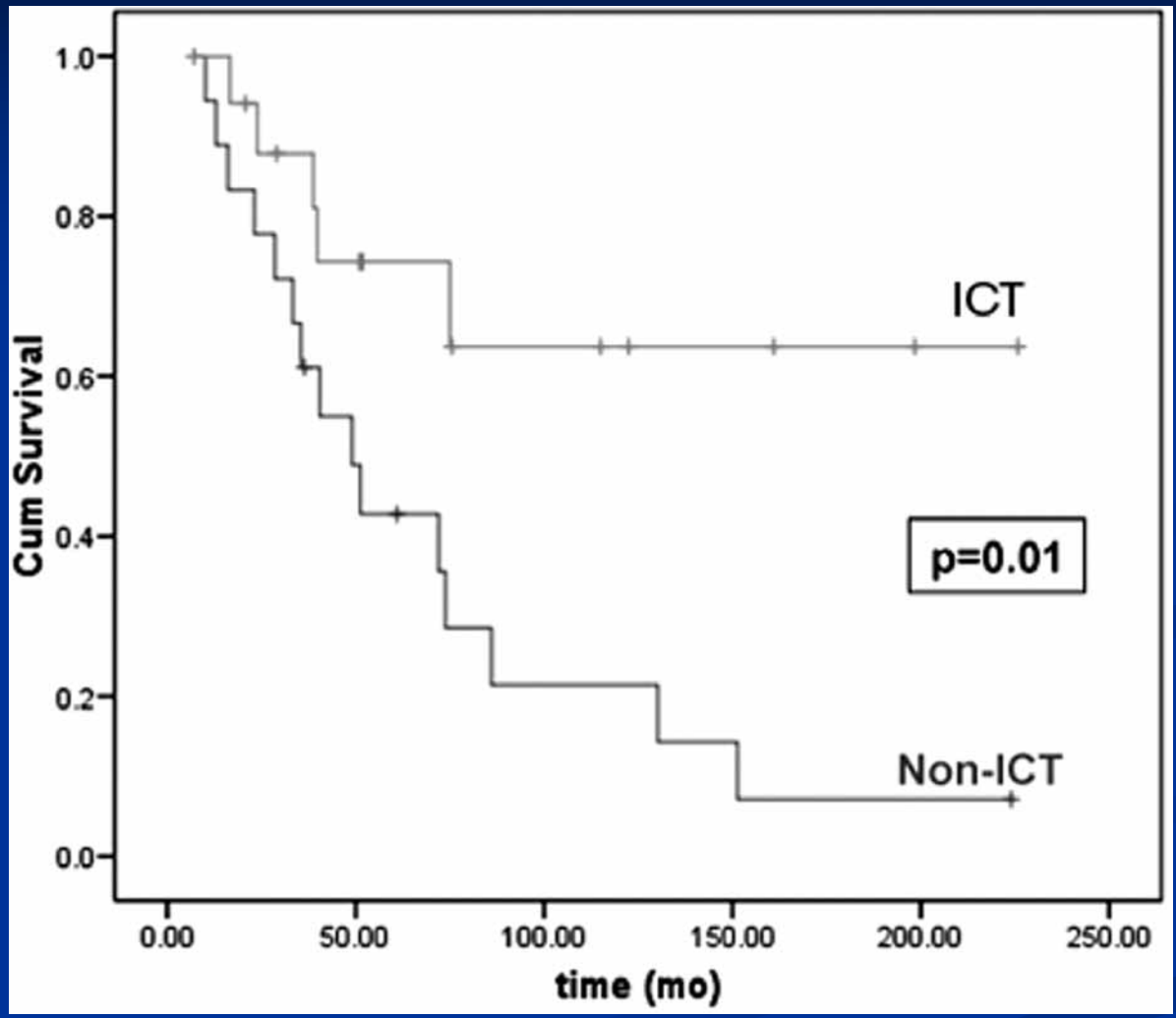
Figure 3. Overall survival in patients with myelodysplastic syndromes (MDS) according to receipt of ICT in a subgroup analysis



Leitch, H. A. et al. Hematology 2009;2009:664-672

Okay, so chelation may improve survival but what about quality of life?

- May decrease transfusion requirements:

  Jensen at al, Br J Haematol 1996

  11 patients: 64% had > 50 % reduction in transfusion requirements, 46% became transfusion independent

How is it that some physicians do not prescribe chelation?

- Data is indeed limited and sometimes ambiguous
- Recall data from Malcovati demonstrating adverse effects of high ferritin in lower risk MDS; those with more advanced disease demonstrated that high ferritin did not significantly alter survival

- Analyses are retrospective with small sample sizes: inherently biased data (patients who were offered and received ICT are likely to be systematically different from those who were not, small numbers may not reflect population)
- Why are all of the consensus guidelines different (experts cannot agree because the data are weak)
- Neither chelator is totally safe (S/E, renal dysfunction, myelosuppression)

What should our physicians be telling us?

- Some data suggest benefit of chelation in terms of survival and quality of life but the data are not perfect
- Canadian Consensus Guidelines exist
- Phase III studies needed to resolve uncertainty
- Keep asking questions

Future Directions

- Randomized controlled trials:
  TELESTO
- Reliable measures of NTBI, LPI, ROS
- Long lasting blood substitutes

Acknowledgement

- Aplastic Anemia and Myelodysplasia Association of Canada
- TOH and CHEO
- Colleagues
- Nurses
- Students and residents
- Patients

Thank you