Transfusional iron overload

Joan Cid, MD, PhD
Dept. of Hemotherapy and Hemostasis, CDB, IDIBAPS
Hospital Clínic
University of Barcelona
Barcelona

jcid@clinic.cat

Transfusional iron overload

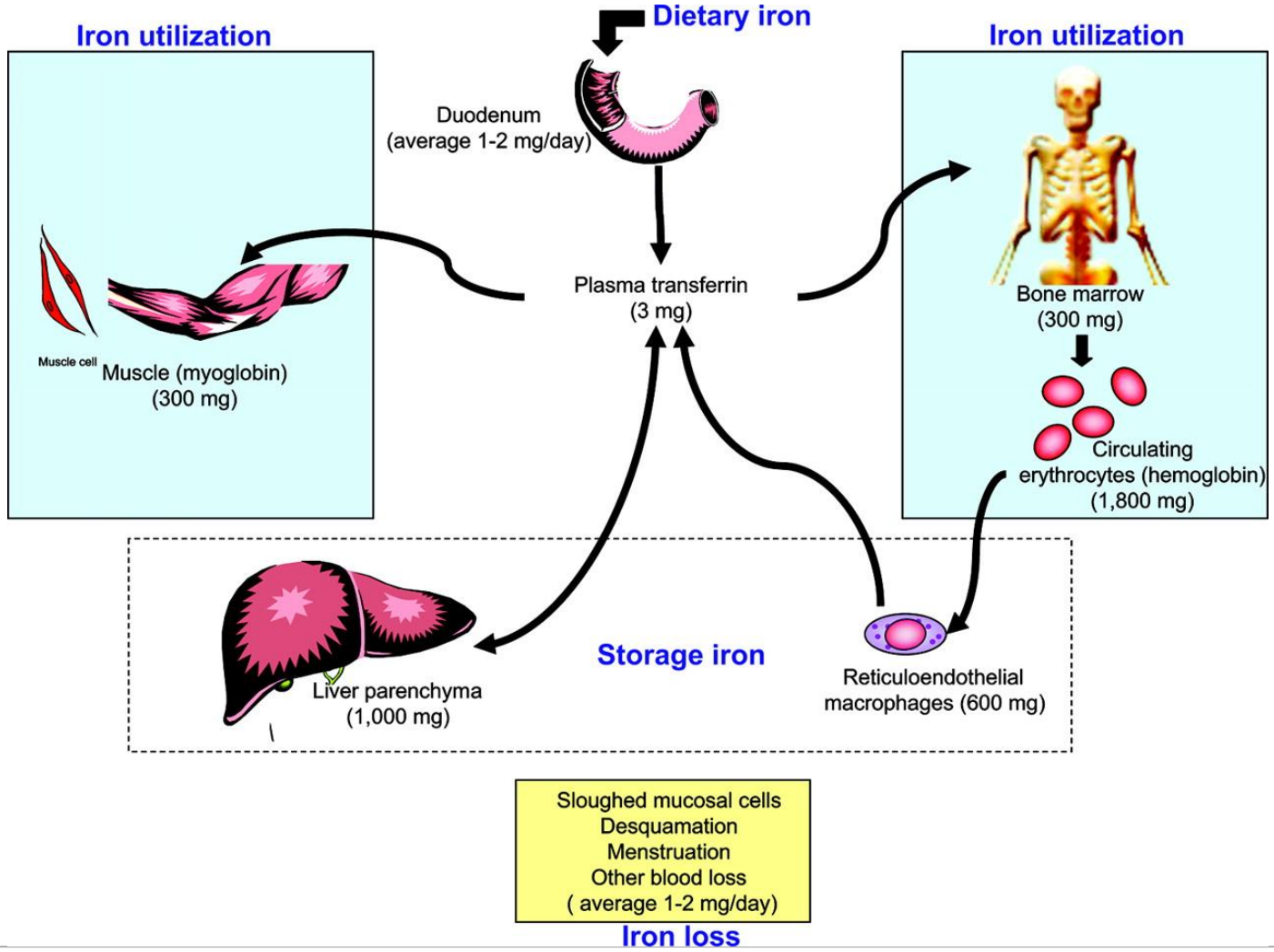
Iron – not enough, or too much

Transfusional iron overload
Iron metabolism

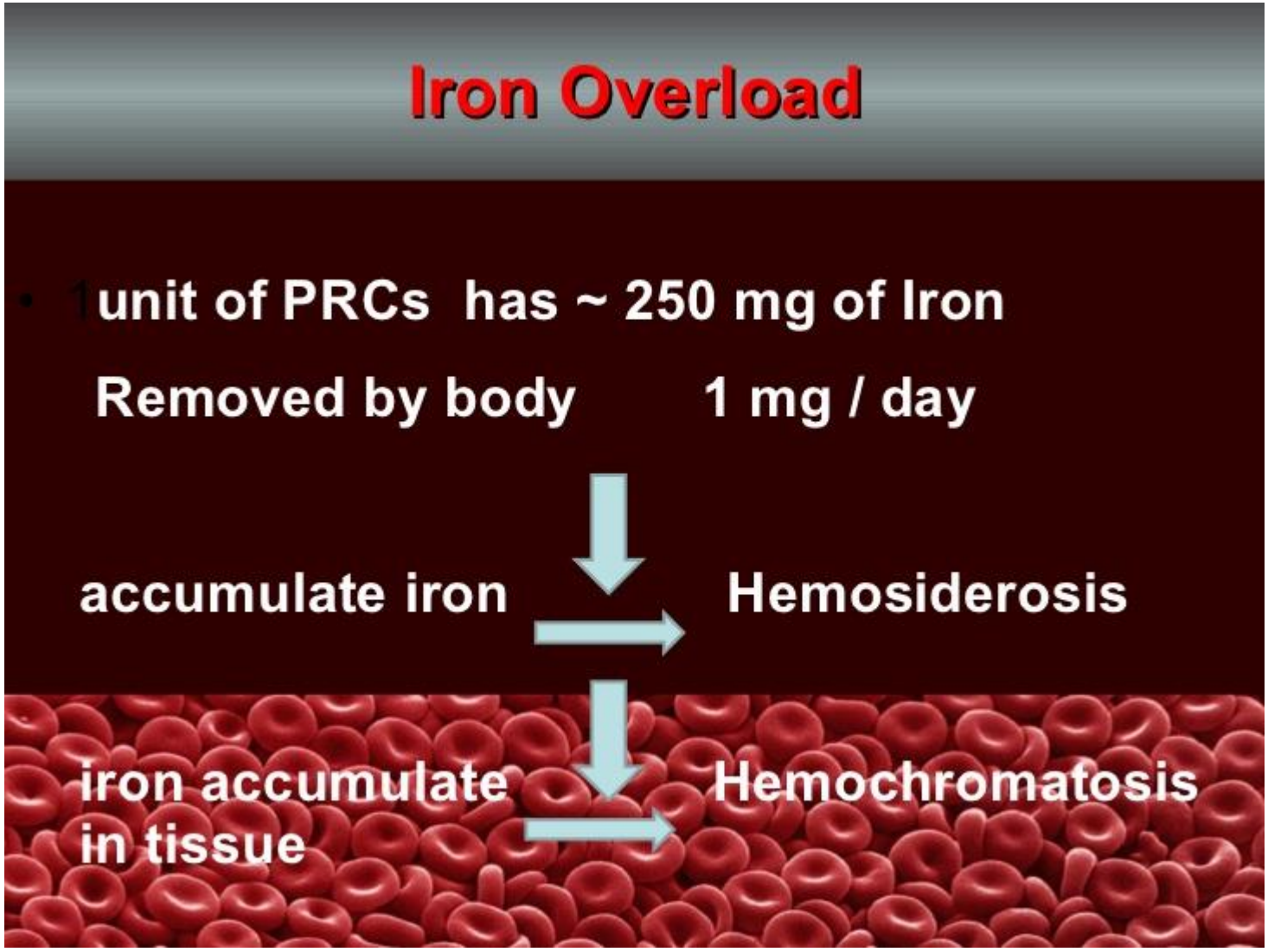
- Iron overload
- Iron toxicity
- Total body iron is tightly regulated:
  - 50 mg/Kg in men
  - 40 mg/Kg in women

Transfusional iron overload

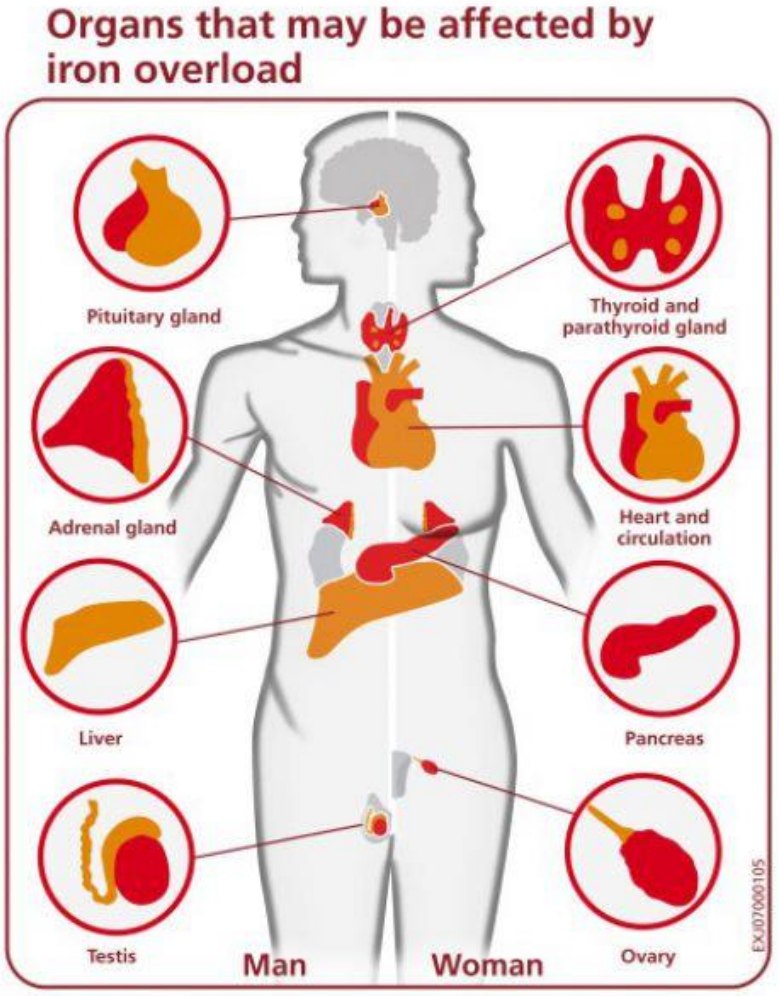
Iron homeostasis



Transfusional iron overload



Transfusional iron overload



Toxic iron builds up across the body and can cause serious damage to vital organs, including the heart and liver.

ORIGINAL PAPER

Vox Sanguinis (2015)

DOI: 10.1111/vox.12367

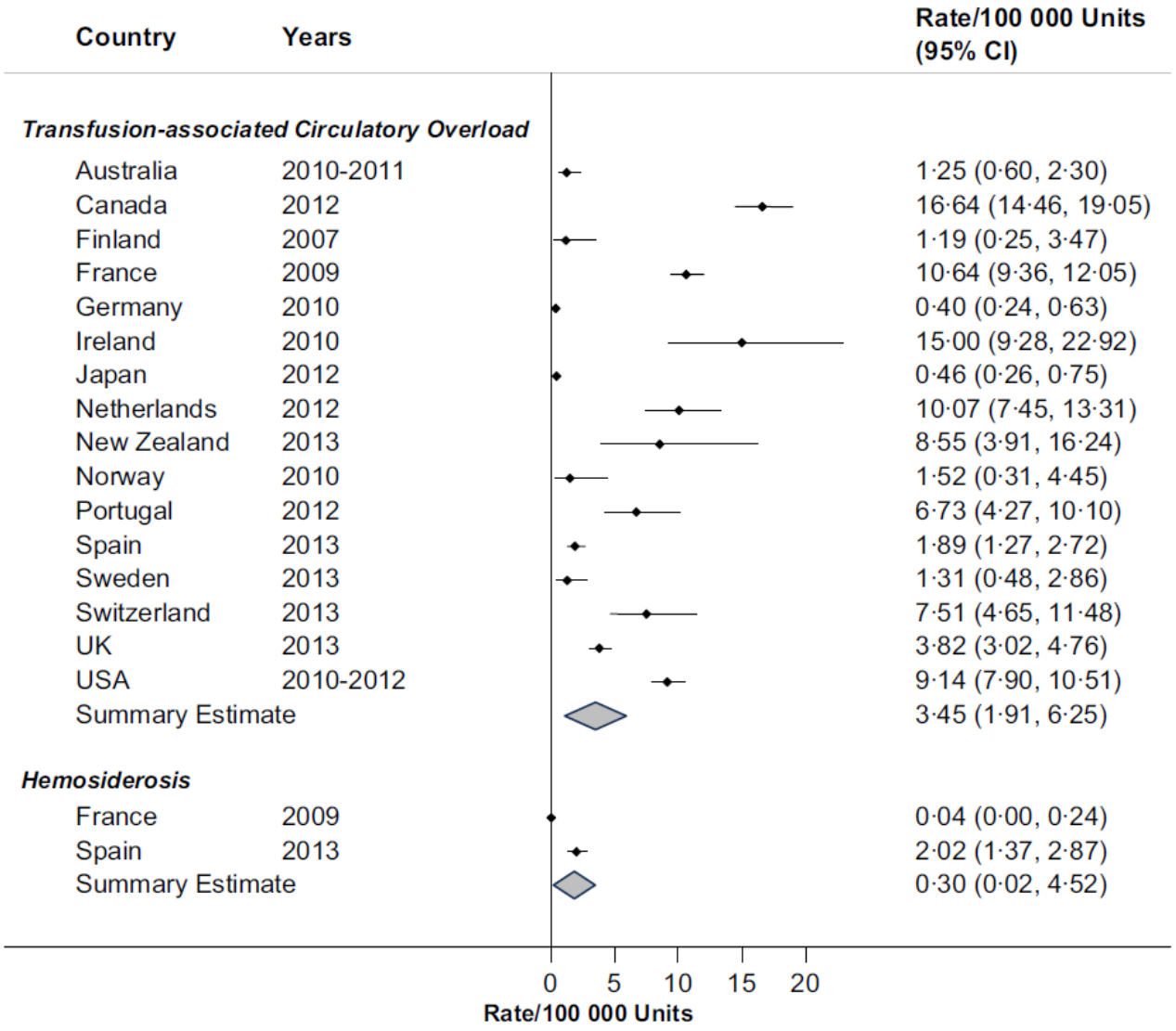
Haemovigilance of reactions associated with red blood cell transfusion: comparison across 17 Countries

M. A. M. Rogers,[1,2] J. M. Rohde[1] & N. Blumberg[3]

[1] *Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, USA*

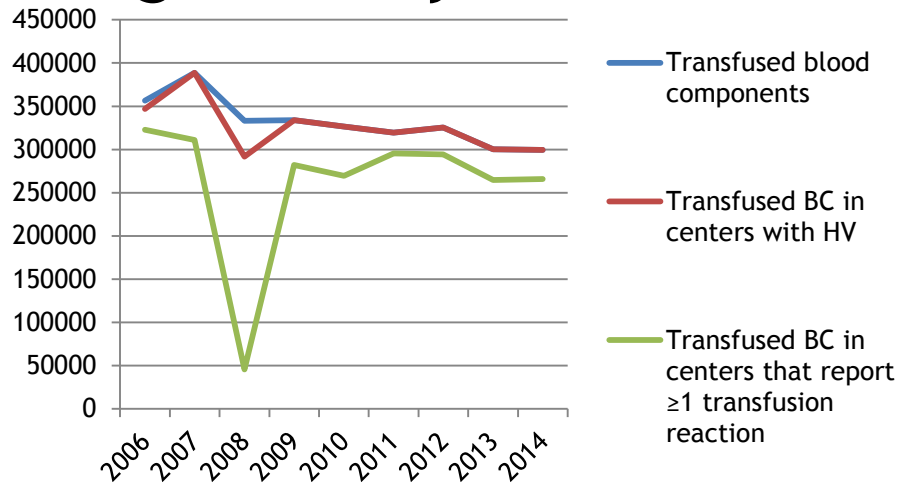
[2] *Patient Safety Enhancement Program, Veterans Administration Ann Arbor Medical Center, University of Michigan, Ann Arbor, Michigan, USA*

[3] *Department of Pathology & Laboratory Medicine, University of Rochester Medical Center, Rochester, New York, USA*

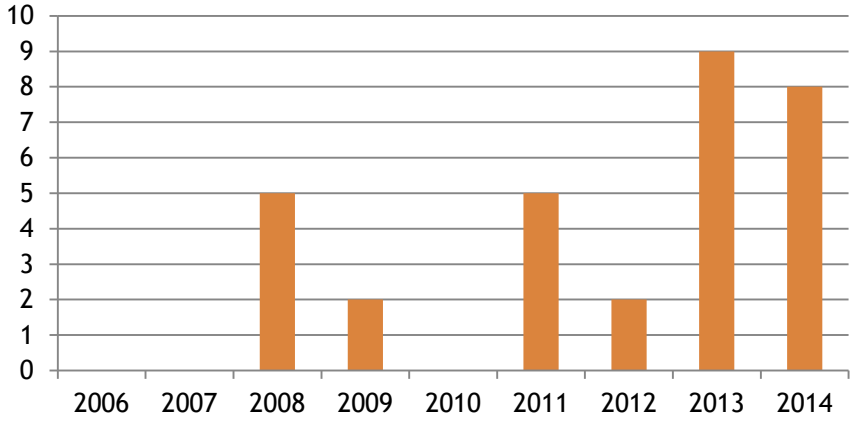


Transfusional iron overload

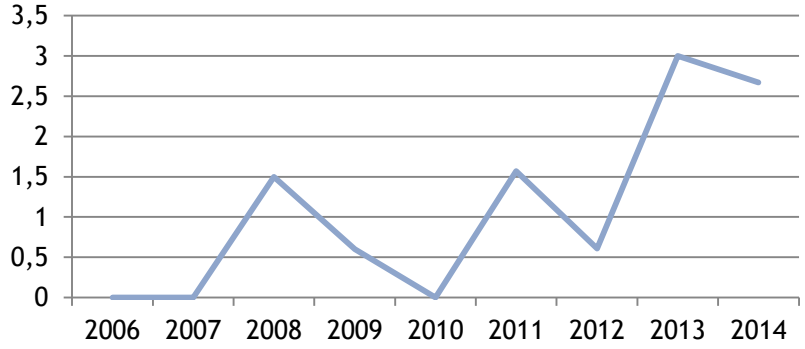
Catalan hemovigilance system



Hemosiderosis



Hemosiderosis (per 100.000 BC)

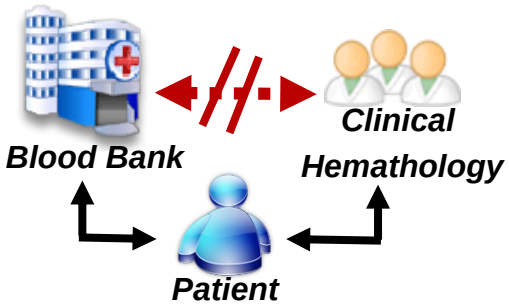


http://www.bancsang.net/receptors/banc-sang/en_hemovigilancia/

BLOODBANK

PROBLEM

- Disconnection between clinicians and blood bank Hematologist.



- Difficult to identify patients at risk
- Low awareness about the risk of IOL
- Only 50% of potential patients are chelated.

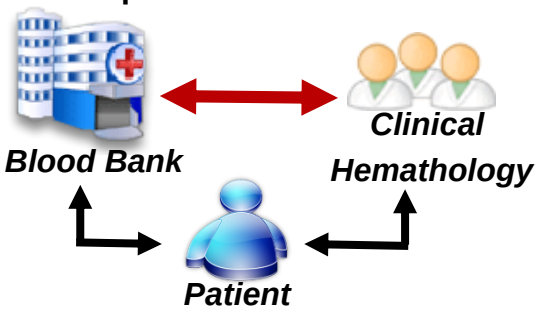
SOLUTION

1. ESTUDIO 20CH
   Identify patients
   Awareness
2. ALARMA 20 CH
   Identify patients
   Monitor
3. *Hemo- survillance Guidelines*
   Call to action SEHH SETS

OUTCOMES

- Facilitate Physicians to:
  - IDENTIFY
  - MONITOR
  - TREAT

  ….patients at risk.



- Increase AWARENESS of the risk of IOL
- PREVENT organ damage

- 49% sales GROWTH YTD

Clinical characteristics and management of iron overload in 631 patients with chronic transfusion dependency: results from a multicentre, observational study

Joan Cid[1], Luis Palomera[2], Matías Díaz[3], Concha Zamora[4], Fernando Solano[5]

ESTUDIO 20CH

- Observational, multicenter study
  - 41 Spanish centers
  - From Nov 2008 to Dec 2009
  - Adult patients who received their first RBC transfusion after Jan 2007, and had received at least 10 RBC units
- 631 patients
  - Male:female ratio (355:267)
  - Median age 69 years (range: 19-97)
  - Hematological disease in 85% patients
    - MDS in 36%
    - AML in 29%

Blood Transfus 2014;12(Suppl 1):s119-23

Clinical characteristics and management of iron overload in 631 patients with chronic transfusion dependency: results from a multicentre, observational study

Joan Cid[1], Luis Palomera[2], Matías Díaz[3], Concha Zamora[4], Fernando Solano[5]

ESTUDIO 20CH

Table II - Transfusion history.

End-point	
Time from diagnosis to first transfusion of RBC units (months), n =559	
Mean (SD)	13 (29)
Time of transfusion dependency (months), n =601	
Mean (SD)	10 (8)
Transfusion rate (days), n =602	
Mean (SD)	26 (44)
Number of RBC units transfused to date, n =631	
Mean (SD)	30 (26)
Patients transfused with ≥20 RBC units	374-59%
Patients transfused with <20 RBC units	257-41%
Number of RBC units transfused in the last year, n =616	
Mean (SD)	18 (18)

RBC: red blood cells; SD: standard deviation.

Blood Transfus 2014;12(Suppl 1):s119-23

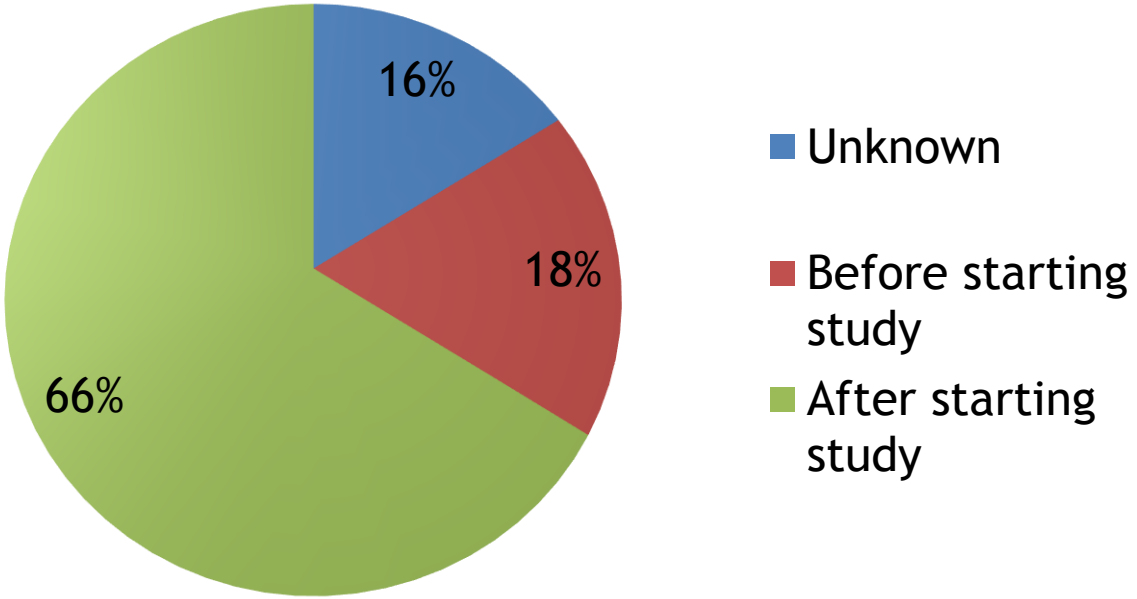
CLÍNIC BARCELONA Hospital Universitari

Clinical characteristics and management of iron overload in 631 patients with chronic transfusion dependency: results from a multicentre, observational study

Joan Cid[1], Luis Palomera[2], Matías Díaz[3], Concha Zamora[4], Fernando Solano[5]

ESTUDIO 20CH

Serum ferritin



Blood Transfus 2014;12(Suppl 1):s119-23

Clinical characteristics and management of iron overload in 631 patients with chronic transfusion dependency: results from a multicentre, observational study

ESTUDIO 20CH

Joan Cid[1], Luis Palomera[2], Matías Díaz[3], Concha Zamora[4], Fernando Solano[5]

Ferritin level at study inclusion (ng/mL), n =528

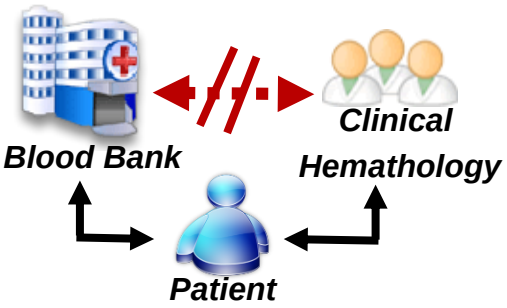
Mean ± SD	1,570±1,557	
N. of patients with ferritin levels ≥1,000 ng/mL	307	58
N. of patients with ferritin levels <1,000 ng/mL	221	42
N. of patients on chelation therapy, n =618	89	14
Indications for chelation therapy, n =89*		
High SF/TSI	78	88
Transfusion of PRBC units	49	55
Other	3	3
Indications for not receiving chelation therapy, n =529*		
Unknown	178	34
Normal SF/TSI	146	28
Comorbidity	83	16
Other	81	15
Advanced age	61	12

Blood Transfus 2014;12(Suppl 1):s119-23

BLOODBANK

PROBLEM

- Disconnection between clinicians and blood bank Hematologist.



- Difficult to identify patients at risk
- Low awareness about the risk of IOL
- Only 50% of potential patients are chelated.

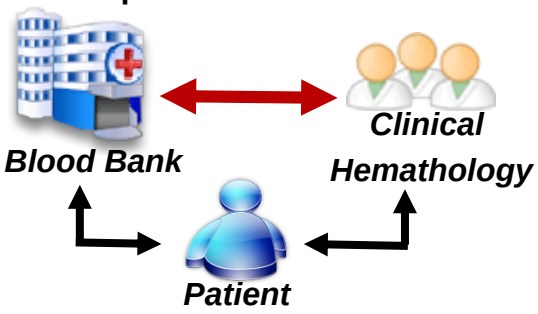
SOLUTION

1. ESTUDIO 20CH
   Identify patients
   Awareness
2. ALARMA 20 CH
   Identify patients
   Monitor
3. *Hemo- survillance Guidelines*
   Call to action SEHH SETS

OUTCOMES

- Facilitate Physicians to:
  - IDENTIFY
  - MONITOR
  - TREAT

  ….patients at risk.



- Increase AWARENESS of the risk of IOL
- PREVENT organ damage

- 49% sales GROWTH YTD

ALARMA 20 CH

➔ Software tool in blood bank computer systems that alerts when chronically transfused patient receives 20 RBC units

Alarm criteria:

Patient >20 RBC/ >5month*

***Patient at risk of organ damage because IOL**

20 CH

Blood Bank

Clinic Hematology

Monitor IOL: SF or TS

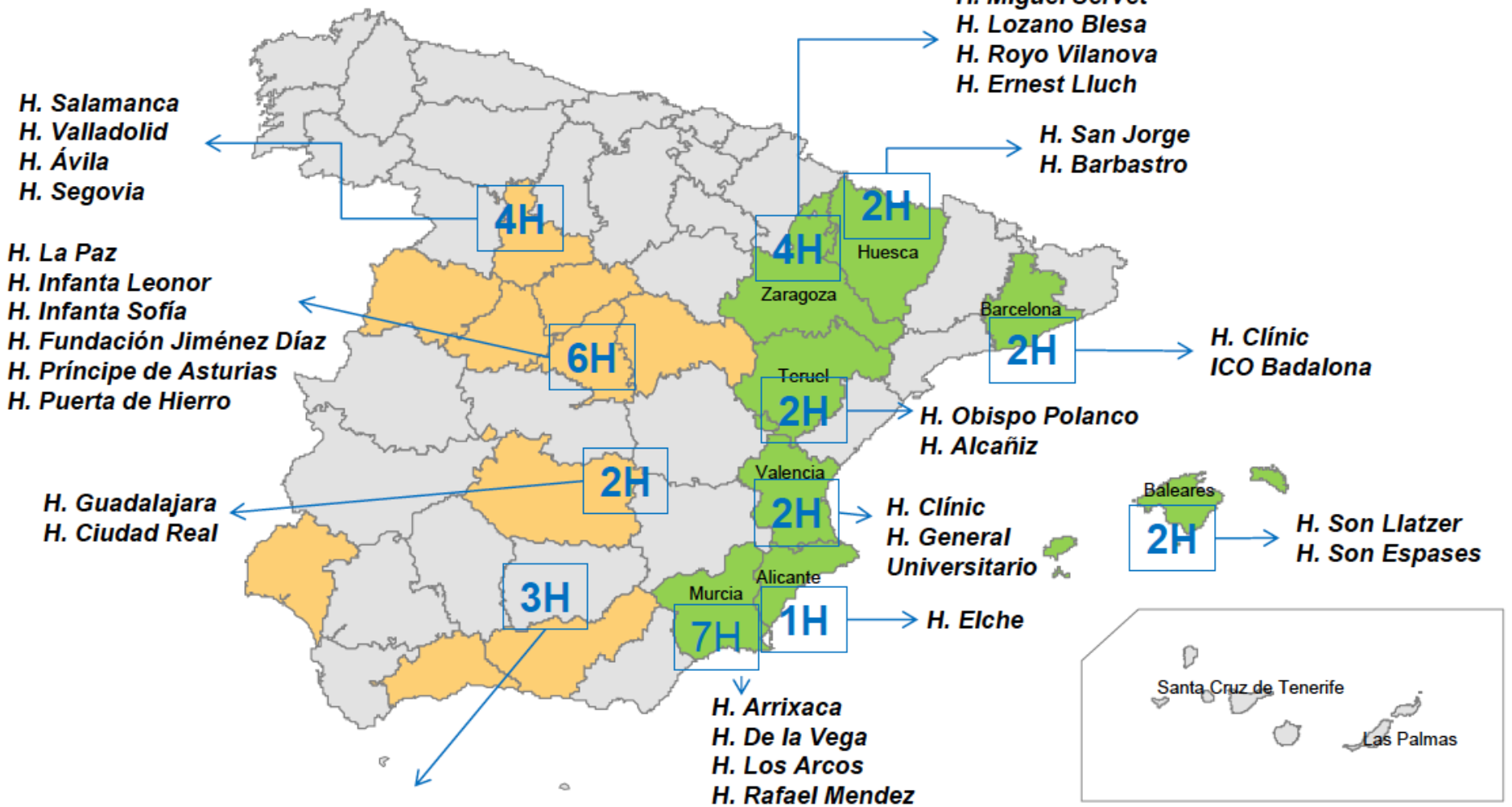
Report to Health authorities

**Considering extend time and include other criteria like pathology.*

Connection between BB and clinicians:

By interface systems or email or print reports

ALARMA 20 CH



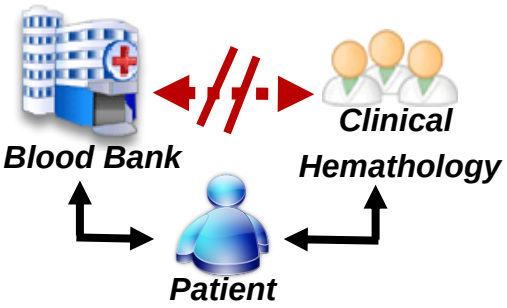
NOVARTIS

CLÍNIC BARCELONA
Hospital Universitari

BLOODBANK

PROBLEM

- Disconnection between clinicians and blood bank Hematologist.



- Difficult to identify patients at risk
- Low awareness about the risk of IOL
- Only 50% of potential patients are chelated.

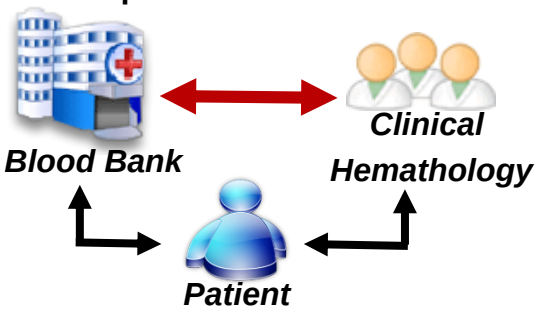
SOLUTION

1. ESTUDIO 20CH
   Identify patients
   Awareness
2. ALARMA 20 CH
   Identify patients
   Monitor
3. *Hemo- survillance Guidelines*
   Call to action SEHH SETS

OUTCOMES

- Facilitate Physicians to:
  - IDENTIFY
  - MONITOR
  - TREAT

  ….patients at risk.



- Increase AWARENESS of the risk of IOL
- PREVENT organ damage

- 49% sales GROWTH YTD

Guidelines on haemovigilance of post-transfusional iron overload

Ángel Remacha[1], Cristina Sanz[2], Enric Contreras[3], Cristina Díaz de Heredia[4], Joan Ramón Grifols[5], Montserrat Lozano[6], Guillermo Martín Nuñez[7], Ramón Salinas[8], Mercedes Corral[9], Ana Villegas[10]

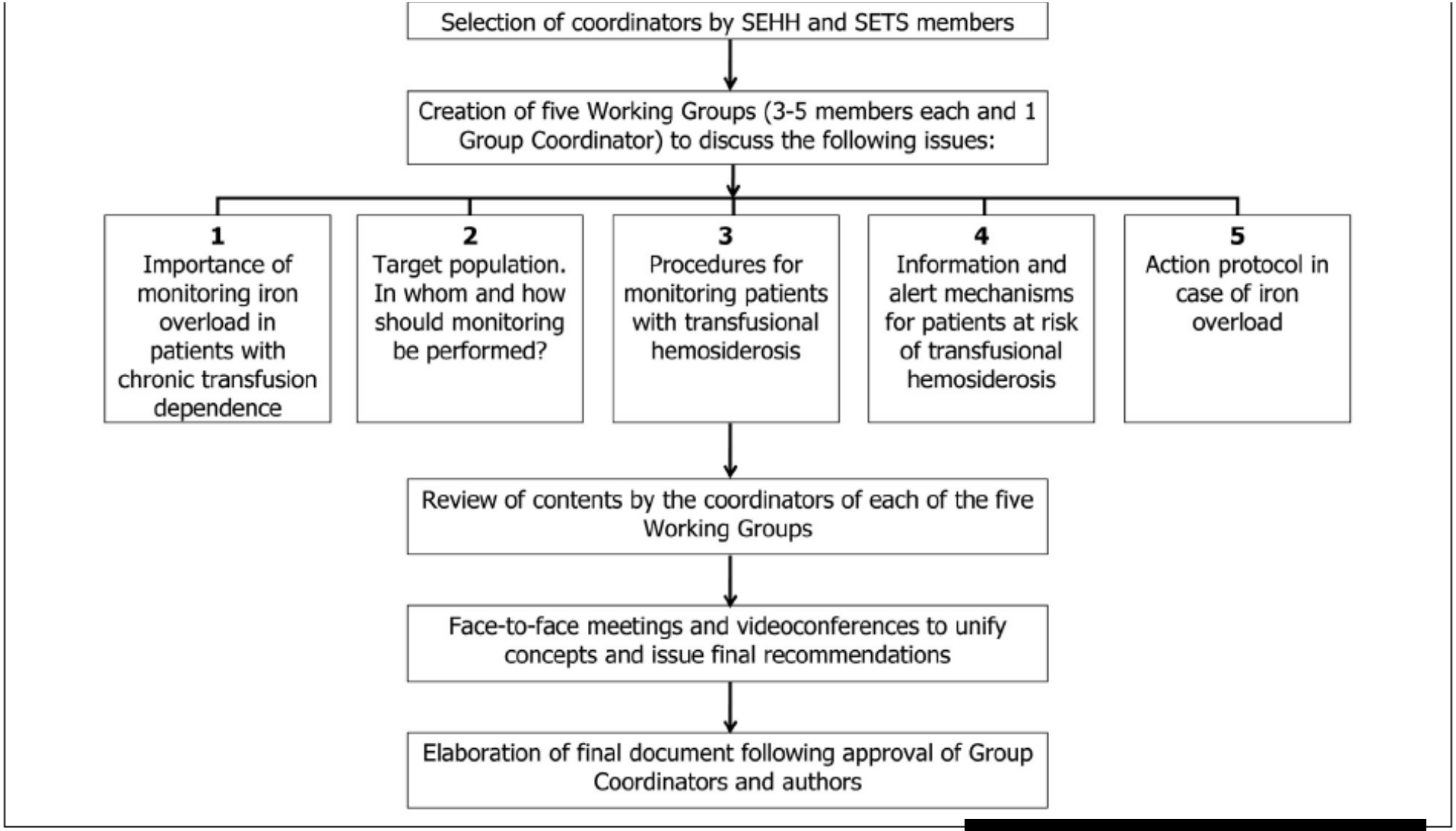


Figure 1 - Process of elaboration of this guideline.

Blood Transfus 2013;11:128-39

Guidelines on haemovigilance of post-transfusional iron overload

Ángel Remacha[1], Cristina Sanz[2], Enric Contreras[3], Cristina Díaz de Heredia[4], Joan Ramón Grifols[5], Montserrat Lozano[6], Guillermo Martín Nuñez[7], Ramón Salinas[8], Mercedes Corral[9], Ana Villegas[10]

- MDS
  - Transfusion dependence is an independent prognostic factor for survival (OS, LFS)
- HPC transplantation
  - Iron overload has been associated with higher frequency of early and late complications

Table I - Diseases associated with chronic transfusion support.

Adult and paediatric patients	Diseases
Haematological diseases	Myelodysplastic syndrome Acute leukaemia Lymphoma Acquired bone marrow aplasia Multiple myeloma
Non-haematological diseases	Malignancies under chemotherapy
Stem cell transplantation	
Ineffective erythropoiesis and congenital haemolytic anaemias	Thalassaemias and haemoglobinopathies Dyserythropoietic anaemias Myelodysplastic syndromes Hereditary spherocytosis and other membrane disorders Pyruvate-kinase deficiency and other enzyme disorders
Congenital aplastic anaemias	Blackfan-Diamond anaemia Fanconi's and other anaemias

Blood Transfus 2013;11:128-39

Guidelines on haemovigilance of post-transfusional iron overload

Ángel Remacha[1], Cristina Sanz[2], Enric Contreras[3], Cristina Díaz de Heredia[4], Joan Ramón Grifols[5], Montserrat Lozano[6], Guillermo Martín Nuñez[7], Ramón Salinas[8], Mercedes Corral[9], Ana Villegas[10]

Table III - Methods used to assess iron overload.

Transferrin saturation index[55]
Assessment of serum ferritin[15]
Measurement of liver iron deposits:
Biopsy[12]
MRI[56]
Study of cardiac iron overload:
Heart function (ejection fraction)[57]
MRI[5,58]

MRI: Magnetic resonance imaging.

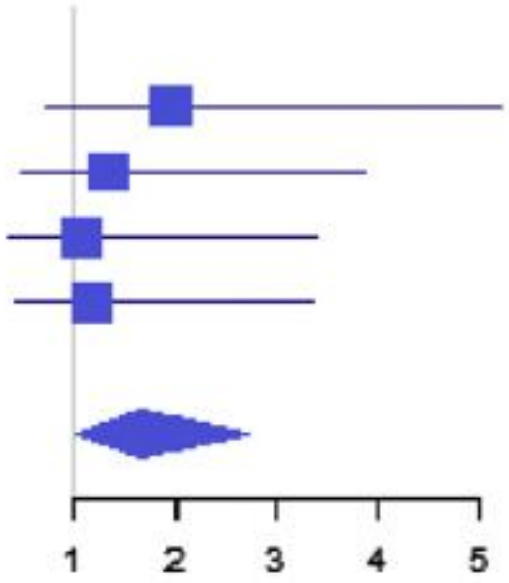
Blood Transfus 2013;11:128-39

Iron Overload in Allogeneic Hematopoietic Cell Transplantation Outcome: A Meta-Analysis

Philippe Armand [1,*], Haesook T. Kim [2], Johanna M. Virtanen [3], Riitta K. Parkkola [3], Maija A. Itälä-Remes [4], Navneet S. Majhail [5], Linda J. Burns [6], Todd DeFor [7], Bryan Trottier [6], Uwe Platzbecker [8], Joseph H. Antin [1], Martin Wermke [8]

C

Center	HR:Random Effects	Weight
DFCI	1.95 (0.73, 5.20)	0.23
Dresden	1.36 (0.48, 3.85)	0.25
Turku	1.08 (0.34, 3.41)	0.36
UMN	1.17 (0.41, 3.37)	0.18
Summary	**1.68 (1.03, 2.73)**	**1.0**



HR for mortality; Ferritin >1000 ng/mL

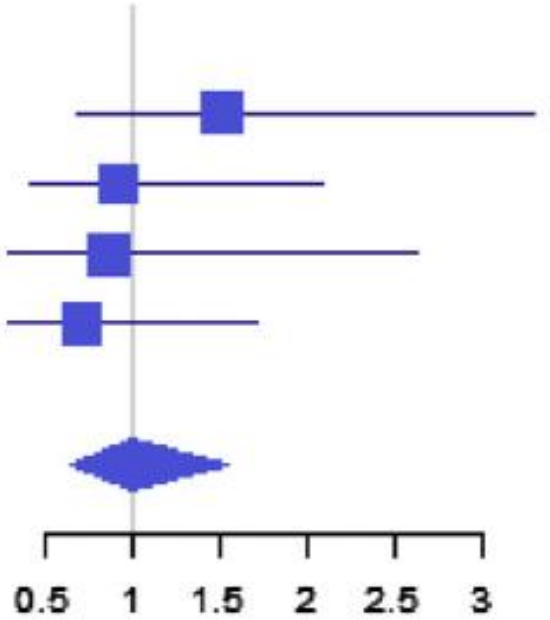
Biol Blood Marrow Transplant 2014;20:1238-57

Iron Overload in Allogeneic Hematopoietic Cell Transplantation Outcome: A Meta-Analysis

Philippe Armand [1,*], Haesook T. Kim [2], Johanna M. Virtanen [3], Riitta K. Parkkola [3], Maija A. Itälä-Remes [4], Navneet S. Majhail [5], Linda J. Burns [6], Todd DeFor [7], Bryan Trottier [6], Uwe Platzbecker [8], Joseph H. Antin [1], Martin Wermke [8]

A

Center	HR:Random Effects	Weight
DFCI	1.50 (0.68, 3.29)	0.32
Dresden	0.91 (0.40, 2.09)	0.28
Turku	0.85 (0.27, 2.62)	0.15
UMN	0.70 (0.28, 1.70)	0.25
Summary	**0.99 (0.63, 1.54)**	**1.0**



HR for mortality; LIC >5 mg/gdw

Biol Blood Marrow Transplant 2014;20:1238-57

Guidelines on haemovigilance of post-transfusional iron overload

Ángel Remacha[1], Cristina Sanz[2], Enric Contreras[3], Cristina Díaz de Heredia[4], Joan Ramón Grifols[5], Montserrat Lozano[6], Guillermo Martín Nuñez[7], Ramón Salinas[8], Mercedes Corral[9], Ana Villegas[10]

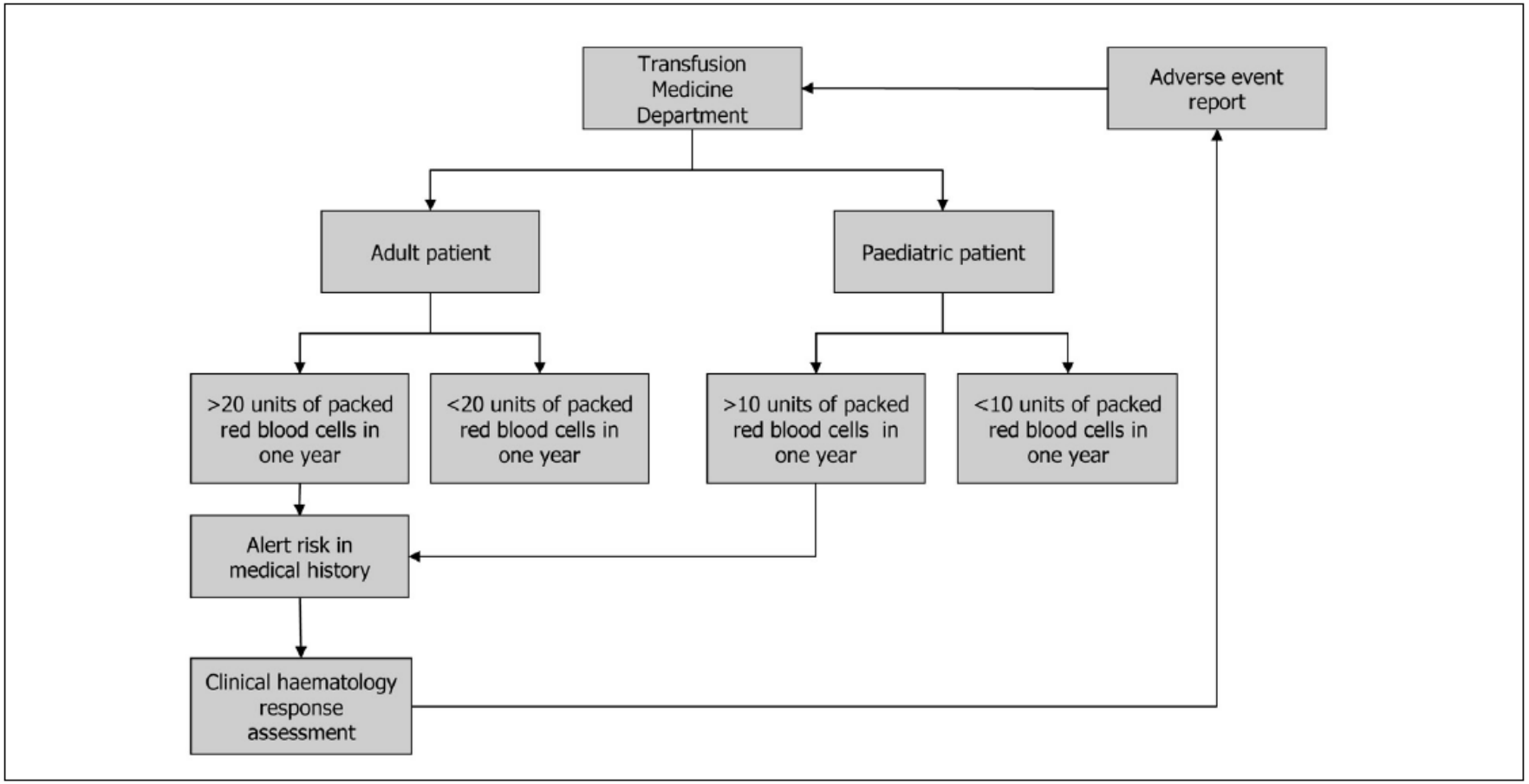


Figure 2 - Algorithm to alert transfusion departments of the risk of transfusion haemosiderosis.

Blood Transfus 2013;11:128-39

Guidelines on haemovigilance of post-transfusional iron overload

Ángel Remacha[1], Cristina Sanz[2], Enric Contreras[3], Cristina Díaz de Heredia[4], Joan Ramón Grifols[5], Montserrat Lozano[6], Guillermo Martín Nuñez[7], Ramón Salinas[8], Mercedes Corral[9], Ana Villegas[10]

Table IV - Characteristics of currently available chelator agents.

	Active substance		
	Deferoxamine	**Deferiprone**	**Deferasirox**
Approved indication	Fe overload in TM >6 years	Fe overload in TM >10 years[1]	Transfusion overload[1]
Dose	25-50 mg/kg/day	75 mg/kg/day	10-30 mg/kg/day
Route of administration	SC infusion 8-10 h/day	Oral/8 h	Oral/24 h
NTBI (24 h)	Persists	Signs detected	Negative
Compliance	Poor	Good	Good
Main adverse effects	Local problems	Agranulocytosis	Renal impairment GI toxicity
Clinical experience in TM	30-40 years	12 years	5 years

Legend
Fe: iron; SC: subcutaneous; NTBI: non-transferrin-bound iron; GI: gastrointestinal; TM: thalassaemia major. [1]When deferoxamine is contraindicated or inadequate.

Blood Transfus 2013;11:128-39

Transfusional iron overload
EPIC trial –deferasirox-

- Prospective, 1-year, multicenter, open-label phase IIIb trial
- Patients ≥2 years-old with transfusional iron overload
  - Serum ferritin ≥1000 ng/mL
  - Serum ferritin <1000 ng/mL and:
    - >20 RBC units transfused
    - Liver hemosiderosis (≥2 mg of Fe/gdw)
- Fixed starting dose of deferasirox and dose titration guided by serum ferritin and safety markers

Cappellini et al. Haematologica 2010;95:557-66

Transfusional iron overload

EPIC trial

Table 1. Demographic and baseline characteristics of the patients.

	Thalassemia (n=1115)	MDS (n=341)	AA (n=116)	SCD (n=80)	Rare anemias (n=43)	Others (n=49)	All patients (n=1744)
Mean age (range), years	18.2 (2-72)	67.9 (11-89)	33.3 (2-79)	23.9 (4-60)	39.5 (2-82)	50.3 (4-83)	30.6 (2-89)
Male:female, n	538:577	204:137	67:49	39:41	20:23	33:16	901:843
Race (Caucasian:oriental:other), n	468:594:53	309:30:2	32:80:4	18:15:47	30:11:2	38:10:1	895:740:109
History of hepatitis B and/or C, n (%)	275 (24.7)	11 (3.2)	8 (6.9)	19 (23.8)	4 (9.3)	2 (4.1)	319 (18.3)
Splenectomy, n (%)	395 (35.4)	13 (3.8)	–	22 (27.5)	12 (27.9)	6 (12.2)	448 (25.7)
Previous chelation therapy, n (%)							
DFO monotherapy	763 (68.4)	137 (40.2)	31 (26.7)	50 (62.5)	24 (55.8)	17 (34.7)	1022 (58.6)
Deferiprone monotherapy	12 (1.1)	14 (4.1)	–	1 (1.3)	1 (2.3)	–	28 (1.6)
DFO + deferiprone	245 (22.0)	24 (7.0)	6 (5.2)	10 (12.5)	5 (11.6)	2 (4.1)	292 (16.7)
Deferasirox	4 (0.4)	1 (0.3)	–	–	–	–	5 (0.3)
None	95 (8.5)	165 (48.4)	79 (68.1)	19 (23.8)	13 (30.2)	30 (61.2)	401 (23.0)
Median duration of previous ICT (25th, 75th percentiles), years	7.8 (2.9,16.1)	1.4 (0.5, 2.6)	2.2 (0.7, 4.4)	6.3 (3.2, 12.4)	1.1 (0.4, 7.0)	1.1 (0.5, 4.5)	5.7 (1.8, 13.5)
Median duration of transfusion therapy (25th, 75th percentiles), years	15.0 (8.0, 23.0)	3.0 (1.0, 4.0)	5.0 (2.0, 8.0)	10.0 (6.5, 17.0)	5.5 (2.0, 14.0)	2.0 (1.0, 6.0)	9.0 (3.0, 19.0)
Mean±SD transfusion sessions in year prior to study entry*	16.6±8.6	24.3±17.7	12.5±13.0	10.7±8.2	21.0±18.7	23.6±20.7	17.8±12.5
Mean±SD total volume of red blood cells transfused in year prior to study entry*, mL/kg	183±133	116±123	116±179	84±57	153±142	148±124	159±136
Median baseline serum ferritin, ng/mL (range)	3188 (462-22320)	2730 (951-9465)	3254 (908-25346)	3163 (579-12835)	3161 (568-13078)	3010 (1173-17053)	3135 (462-25346)

*Information on the number of transfusions is only available for the year prior to study entry. DFO, deferoxamine; ICT, iron chelation therapy.

Cappellini et al. Haematologica 2010;95:557-66

Transfusional iron overload
EPIC trial

	Thalassemia	MDS	AA	SCD	Rare anemias	Others	All patients
All patients							
Baseline	3188	2730	3254	3163	3161	3010	3135
	(462-22320)	(951-9465)	(908-25346)	(579-12835)	(568-13078)	(1173-17053)	(462-25346)
Change from baseline*	-163	-253	-964	-225	-832	-620	-264
	(-10282 to 9501)	(-7125 to 14145)	(-15704 to 13894)	(-3728 to 2846)	(-4522 to 7064)	(-8846 to 4285)	(-15704 to 14145)
	n=1104	n=321	n=115	n=78	n=42	n=47	n=1707
P versus baseline*	<0.0001	0.0019	0.0003	0.2588	0.0275	0.0235	<0.0001

**Based on last-observation-carried-forward (LOCF) analysis. Presented serum ferritin values are median (range).*

Cappellini et al. Haematologica 2010;95:557-66

Transfusional iron overload
EPIC trial

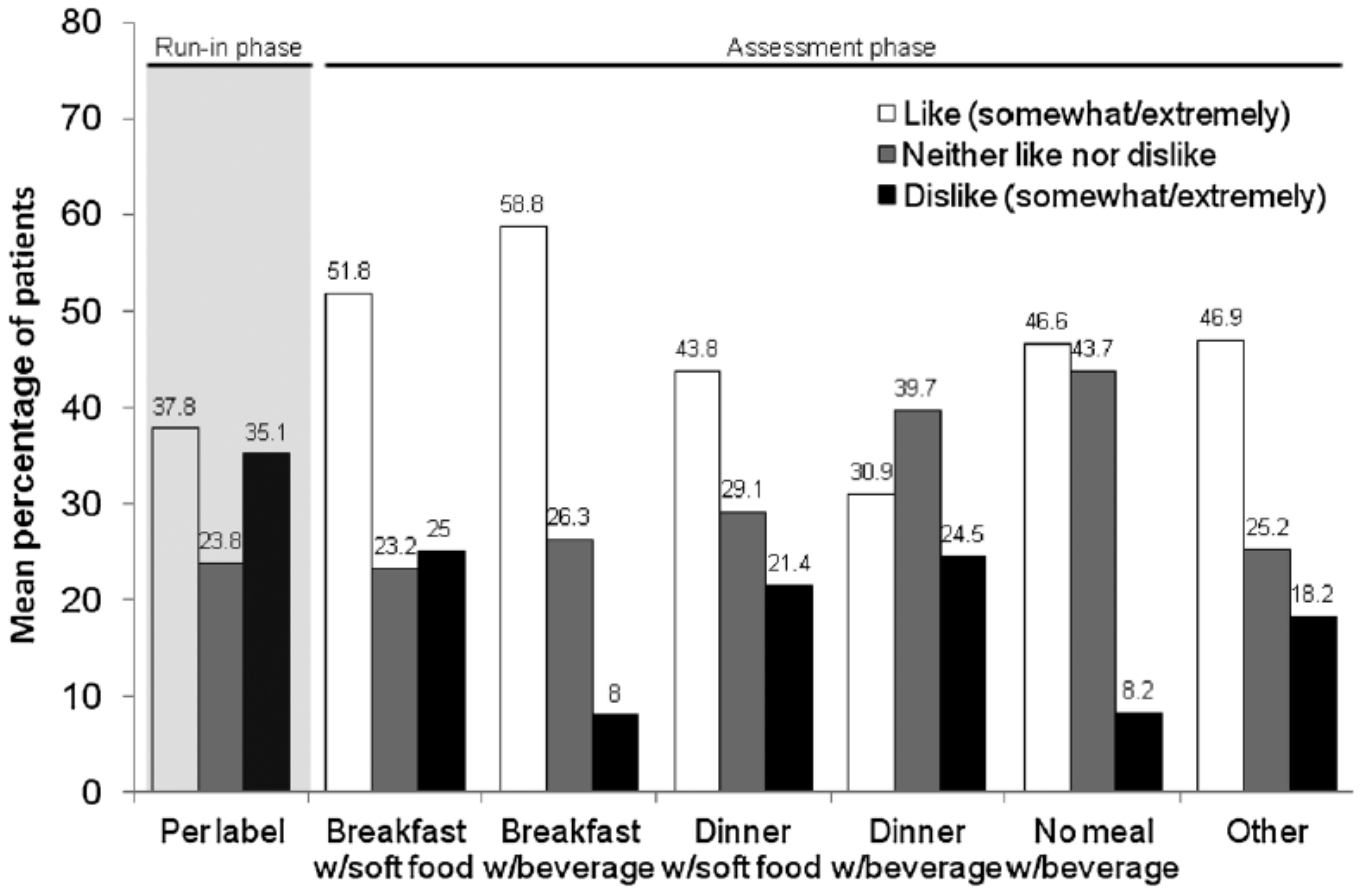
Table 4. Safety results by underlying disease.

Adverse events, n (%)	Most common (>3%) drug-related adverse events						
	Thalassemia (n=1115)	MDS (n=341)	AA (n=116)	SCD (n=80)	Rare anemias (n=43)	Others (n=49)	All patients (n=1744)
Diarrhea	87 (7.8)	111 (32.6)	18 (15.5)	9 (11.3)	13 (30.2)	13 (26.5)	251 (14.4)
Skin rash	129 (11.5)	23 (6.7)	13 (11.2)	3 (3.7)	4 (9.3)	2 (4.1)	174 (10.0)
Nausea	42 (3.8)	45 (13.2)	26 (22.4)	5 (6.3)	9 (20.9)	8 (16.3)	135 (7.7)
Abdominal pain	54 (4.8)	26 (7.6)	7 (6.0)	1 (1.3)	6 (14.0)	3 (6.1)	97 (5.6)
Upper abdominal pain	25 (2.2)	25 (7.3)	7 (6.0)	5 (6.3)	4 (9.3)	2 (4.1)	68 (3.9)
Vomiting	20 (1.8)	26 (7.6)	10 (8.6)	3 (3.7)	4 (9.3)	3 (6.1)	66 (3.8)

Cappellini et al. Haematologica 2010;95:557-66

The Palatability and Tolerability of Deferasirox Taken With Different Beverages or Foods

Stuart L. Goldberg, MD,[1]* Patricia J. Giardina, MD,[2] Deborah Chirnomas, MD,[3] Jason Esposito, MSHS,[4] Carole Paley, MD,[4] and Elliott Vichinsky, MD[5]



Goldberg et al. Pediatr Blood Cancer 2013;60:1507-12

Therapeutics and Clinical Risk Management

Dovepress

open access to scientific and medical research

Open Access Full Text Article

REVIEW

Evaluation of a new tablet formulation of deferasirox to reduce chronic iron overload after long-term blood transfusions

Table 2 Iron chelator properties

	Deferoxamine	Deferiprone	Deferasirox (Exjade®)	Deferasirox (Jadenu®)
FDA approval	1968	2011	2005	2015
Administration	SQ or IV	Oral tablets	Oral tablets dissolved in liquid	Oral tablets
Dosing frequency	daily for 5–7 days/week (if SQ)	Three times a day	Once daily	Once daily
Usual initial dose in chronic iron overload[a]	SQ: daily dose of 1,000–2,000 mg or 20–40 mg/kg/day[b] IV: 40–50 mg/kg/day[c]	25 mg/kg (for a total daily dose of 75 mg/kg)	Transfusional iron overload: 20–40 mg/kg NTDT: 10–20 mg/kg	Transfusional iron overload: 14 mg/kg NTDT: 7 mg/kg
Administration with food	N/A	May be taken with or without food	Empty stomach	Empty stomach or with a low-fat meal
Common adverse effects	Infusion site reactions, gastrointestinal disturbances, renal insufficiency	Gastrointestinal disturbances, LFT abnormalities, arthralgia, neutropenia	Gastrointestinal disturbances, renal insufficiency, rash, LFT abnormalities	Gastrointestinal disturbances, renal insufficiency, rash, LFT abnormalities

Notes: [a]Dosing as indicated for adult patients; [b]administered over 8 to 24 hours; [c]administered over 8 to 12 hours for 5 to 7 days per week.

Abbreviations: SQ, subcutaneous; IV, intravenous; NTDT, non-transfusion-dependent thalassemia; LFTs, liver function tests; FDA, United States Food and Drug Administration; N/A, not applicable.

Transfusional iron overload

Conversion from Exjade® to Jadenu®

EXJADE (deferasirox) Tablets for Oral Suspension

JADENU (deferasirox) Tablets

EXJADE® DOSE (mg/kg/day)	JADENU™ DOSE (mg/kg/day)
20	14
30	21
40	28

Transfusional iron overload
Conclusions

- Iron overload from chronic RBC transfusion therapy is underdiagnosed
- Morbidity and mortality, mainly from cardiotoxicity, is associated with transfusional iron overload
- Screening for iron overload by serial measurements of serum ferritin is recommended
- Iron chelator treatment should start early to decrease the morbidity and mortality from iron toxicity