The role of haemovigilance in monitoring transfusion transmissible infections and other adverse reactions in chronically transfused patients

Constantina Politis

Coordinating Haemovigilance Centre (SKAE)

Athens, Hellas

15 IHS – Brussels 2013

Contents

- **Transfusion dependent patients**

  - Definition, diagnostic categories
  - Guaranteeing adequacy, safety and quality

- **The risk of transfusion in the chronically ill**

  - TTIs, alloimmunization, haemosiderosis

- **Thalassaemia as a model disease**

- **Lessons learnt from Haemovigilance procedures**

  - Preventive and corrective measures

  - Future plans within IHN - ISTARE

Part I

- Transfusion dependent patients
- The risk of transfusion in the chronically ill

Transfusion–dependent patients

Definition

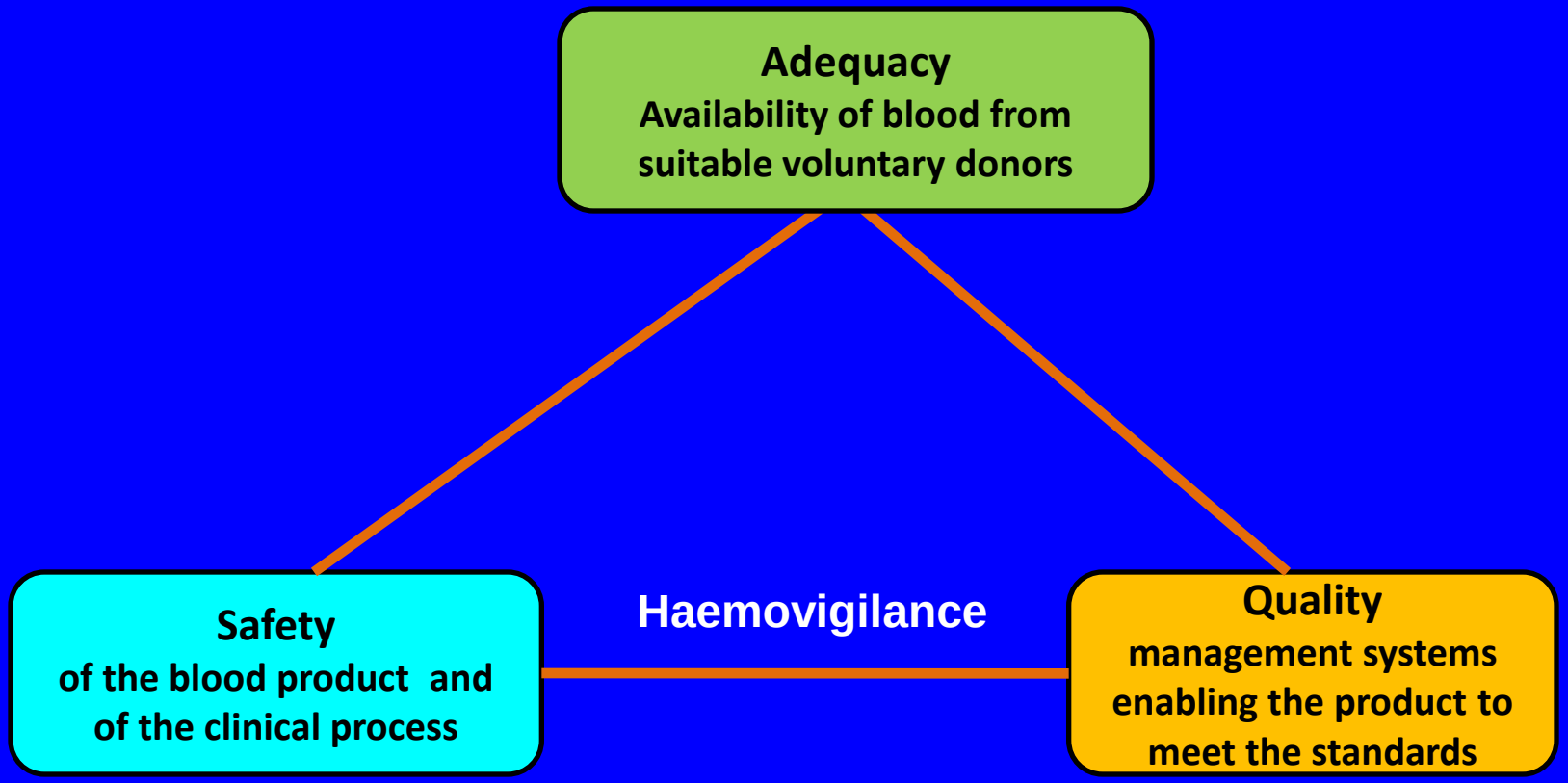
Patients requiring frequent and long-term transfusion support to sustain life

Diagnostic categories

- **Thalassaemia major** *regular transfusion required from early childhood*
- **Sickle cell disease** *transfusion should be performed for strict indications*
- **Severe aplastic anaemia** *repeated transfusions may be required*
- **PNH** *repeated transfusion may be required*
- **Myelodysplasias** *regularly transfused >70 years of age*
- **Other hereditary or acquired chronic anaemias**

Mortality and Morbidity varies

The targets of transfusion



Blood transfusion and the regulatory framework

2002/98/EC → *setting standards of quality and safety*

2004/33/EC → *some technical requirements including blood testing*

2005/61/EC → *traceability and notification of serious adverse reactions/events*

2005/62/EC → *quality specifications*

Council of Europe

"Guide to the preparation, use and quality assurance", 16th edition

- *Identification of patients at blood sampling, Serological investigations,*
- *Compatibility, Pre-transfusion and Transfusion measures*
- *Clinical surveillance, Haemovigilance procedures*

WHO Global Forum for blood safety - Global Consultation on HV

Chronic transfusion exposes the patient to various risks

Alloimmunisation, Disease transmission, Haemosiderosis

The level of risk depends on:

- **the time of onset of transfusion**
- **the quality of the transfused product**
- **appropriateness of performance**
- **the number of the units transfused**

Patients with hereditary haemolytic anaemias requiring chronic transfusion from early childhood, are at a higher risk than patients suffering from myelodysplasias and other hematological/oncological diseases.

Policies for the provision of Red Cells for transfusion dependent patients

Guaranteeing safe blood of good quality requires the implementation of additional and more stringent technical requirements than those imposed in the European legislation

Special problems for transfusion dependent patients

- Alloimmunisation in red cell antigens
- Difficulty in assigning antibody specificity
- Variation of the volume of RBC in each unit transfused
- Age of red cell units

  Recent literature on the association between duration of storage of transfused RBCs and morbidity and mortality in patients is inconclusive.

- Adverse reactions to cytokines or to antibodies HLA antigens of the donors leucocytes

Policies for the provision of Red Cells for transfusion dependent patients

Recommendations

- Extended RBC phenotyping
- RBC antigen matching
- Selection of RBC units with the greatest volume to minimise exposure
- Age of RBC units
  - < 2 weeks old for maximum survival in the patients' circulation
  - For exchange transfusions in SCD < 7 days old to minimise ARs of plasma K in stored blood
- In PNH patients washed cells are not required to avoid complement mediate lysis

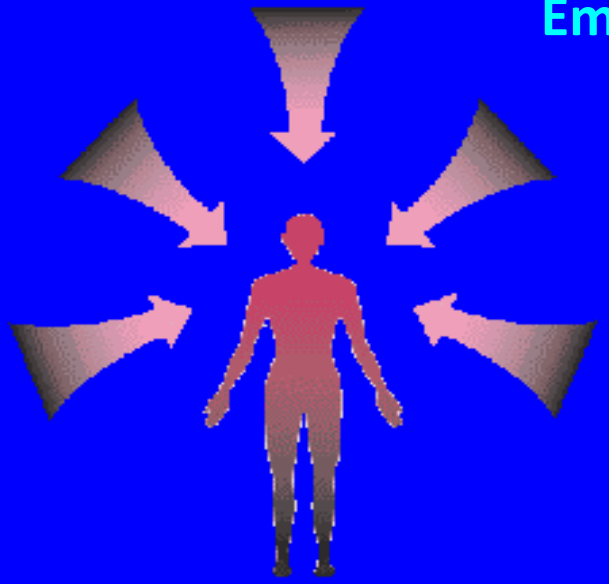
NHSBT (2011)

Other Risks

Bacteria
Introduced during collection

Leukocytes
Adverse immune responses and transfusion reactions

Emerging/Unknown Viruses



Known Pathogens
For which no assay is available

Window Period
Limits of detection of current assays (e.g. false negatives)

Transfusional iron overload

The dual power of blood

Euripides 2500 BC

Part II

- Thalassaemia as a model disease
- The role of haemovigilance in monitoring TTIs and other adverse reactions in the chronically transfused

Thalassaemia as a model disease

- Thalassaemia major can be taken as a model disease in order to describe the protocol of transfusion and the necessary measures to prevent transfusion associated adverse reactions in the chronically transfused and other specific groups of patients in need of transfusion.

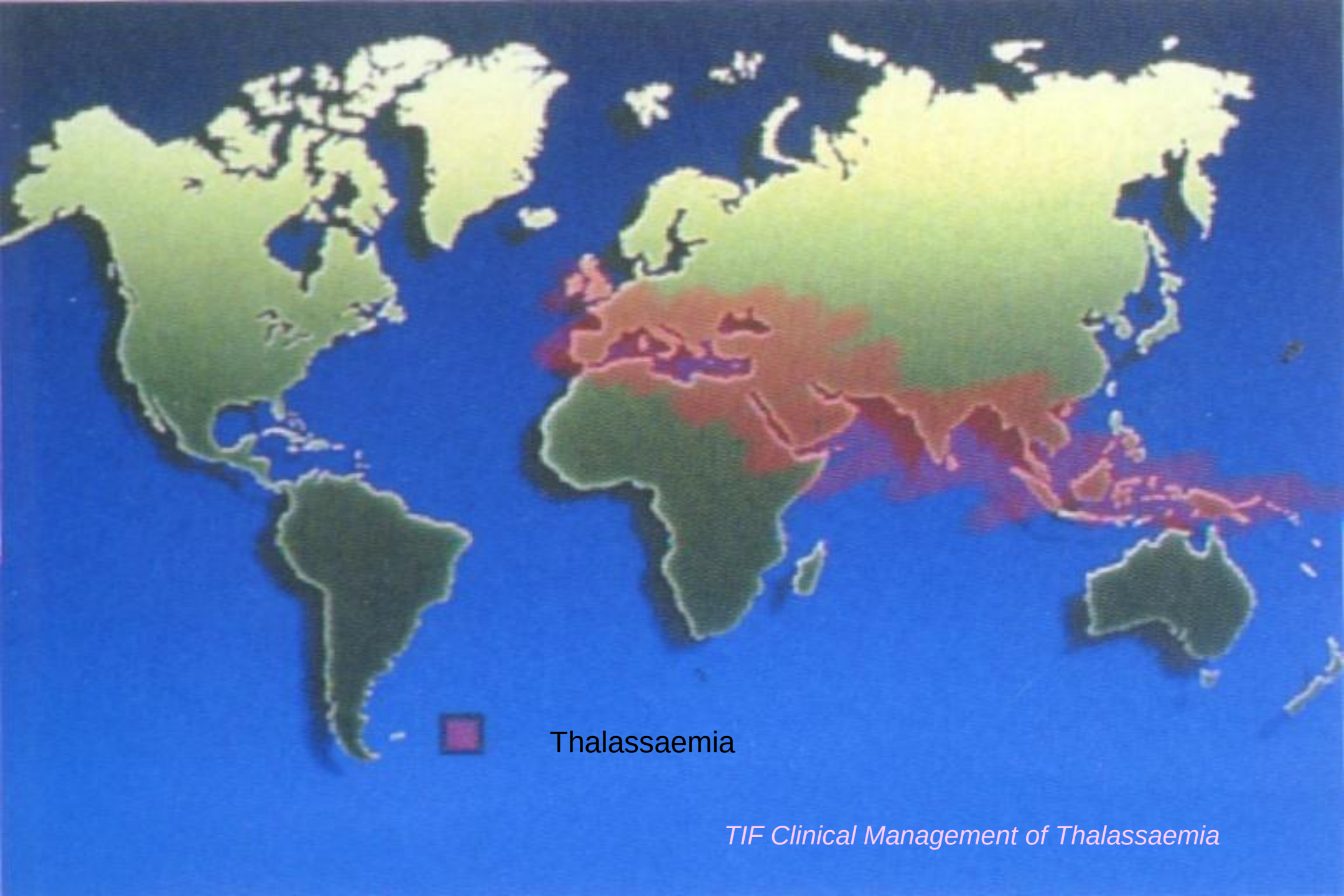
Global Data on Thalassaemias

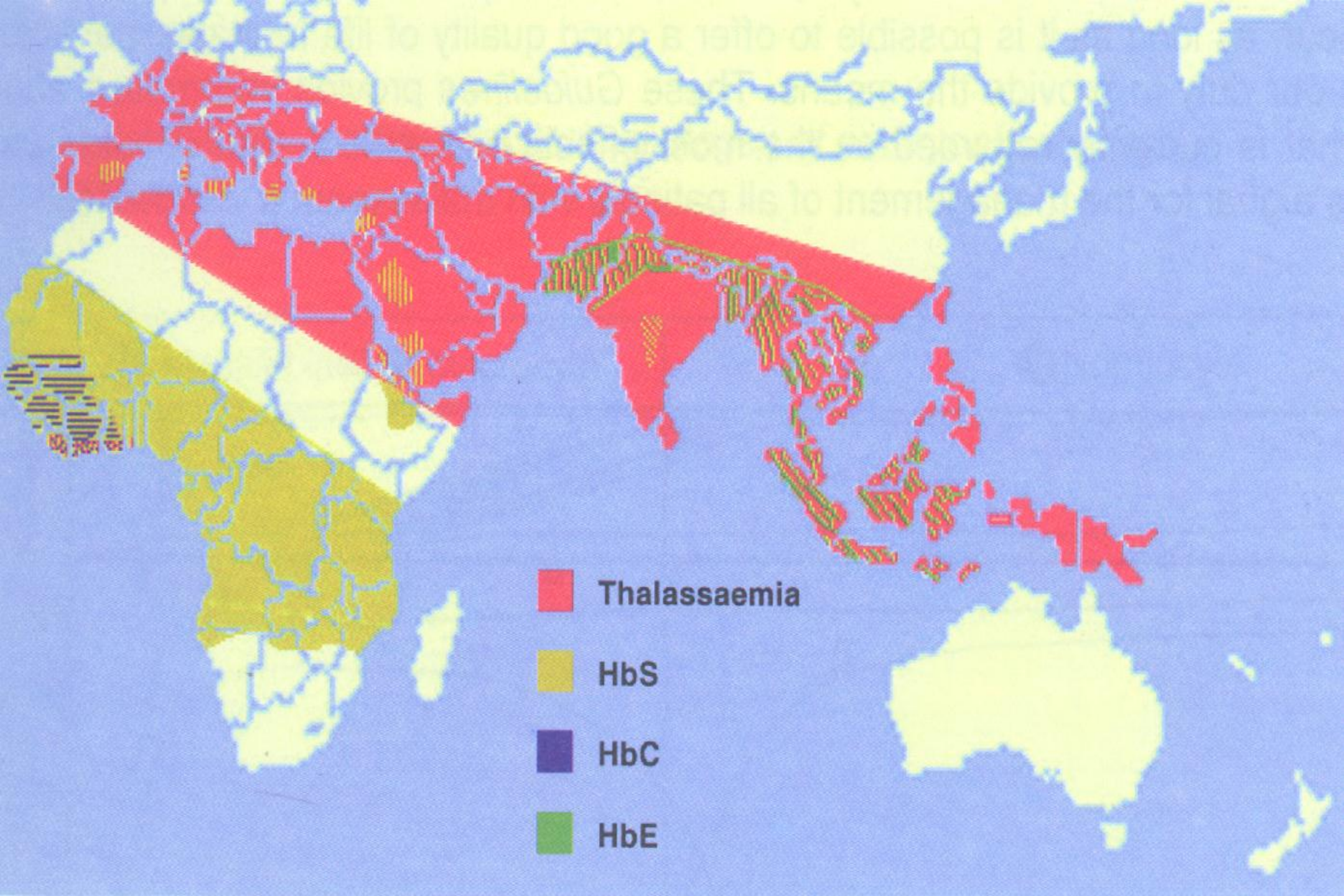
WHO

- **1.5% of the population (80 million) are carriers of β-thalassaemia**
- ***60,000 affected children born annually***
- **5% of the population (266 million) are carriers of β-thalassaemia, sickle cell and HBE/β-thalassaemia**

TIF

- ***200,000 patients are alive and registered as receiving treatment***


Thalassaemia


Thalassaemia
HbS
HbC
HbE

Italy, Greece, Cyprus, Turkey have large numbers of patients

Total no. of patients	30,000 approximately
Mean age	> 18 years
Blood needs	> 1,000,000 units/annually

Thalassaemia International Federation (TIF)

Thalassaemia

A compound Greek word

Θάλασσα - Thalassa (sea)

Αναιμία – Anaemia (no blood)

Thalassaemia

Crete ≈8,000 BC

Archaeological evidence of thalassaemia in the bone lesions (symmetrical porotic hyperostosis) of the skeleton of a 17 year old female buried in the village of Archanes

Angel GI , in Brothwell and Sandison : Diseases in Antiquity, Springfield Ill, Charles C Thomas, 1967

The cornerstone of treatment

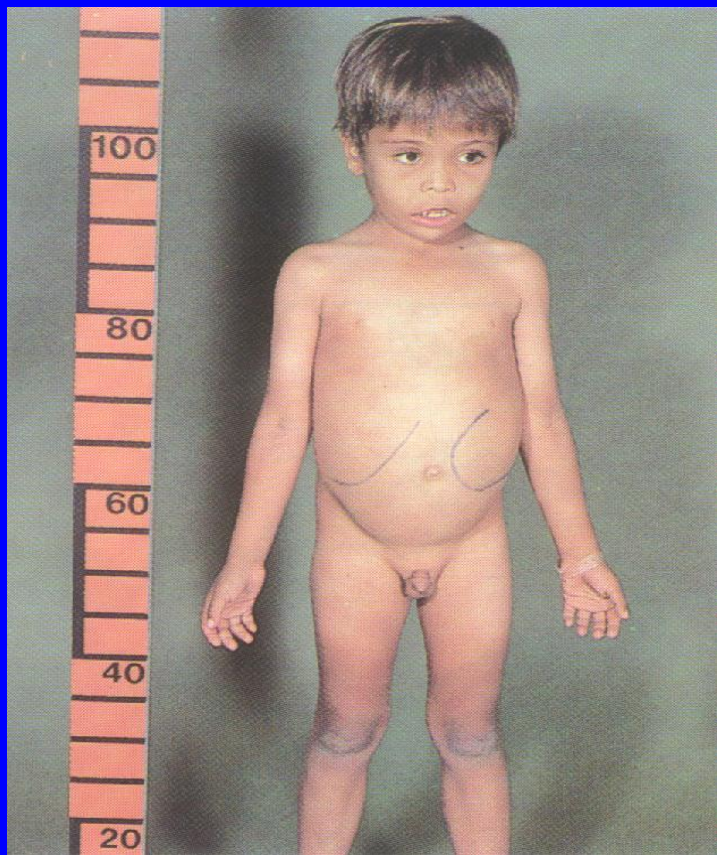
Despite progress in the management of the disease, regular blood transfusion from early childhood remains the cornerstone of treatment.

Effective transfusion therapy

- Requires adequate and safe blood
- Allows normal physical activity
- Improves growth and pubertal development
- Prevents bone marrow malformation
- Prevents organomegaly
- Increases survival
- Improves quality of life

If thalassaemic patients are not transfused effectively, the severe anaemia and the over-expansion of bone marrow due to ineffective erythropoesis can lead to

- Poor growth
- Bone deformities
- Organomegaly
- Impairment of normal physical activities
- Death during the second decade of life



7 year-old boy

Blood Requirements in Thalassaemia major

Depend upon

- The molecular basis of thalassaemia
- The patient's age
- The clinical condition
  (splenectomy, alloimmunization, other)
- The transfusion regime

1-2 units of RBCs every 2-4 weeks
for moderate transfusion regime
(pre-transfusion Hb 9.5 – 10 g/dl)

It allows effective prevention of iron loading.

It permits spontaneous pubertal development in contrast with hypertransfusion regiments once favored

Measures for Optimal transfusion therapy

For the transfused RCCs

- Fresh (debated issue) and leucodepleted
- Washed, irradiated (when appropriate)
- Other advances
  - Nutrient additives, Automated washing
  - End-to-end electronic system
  - Molecular genotyping for extended matching
  - Erythroapheresis, Pathogen inactivation

For the patient

- Use of donor RC with a normal recovery and half-life in the recipient
- Assurance of sufficient O_2 transportation
- Achievement of an appropriate Hb
- Avoidance of adverse reactions

Monitoring blood transfusion indices

- Hb
- Volume and Ht of blood units
- Annual requirements
- Daily Hb fall
- Mean transfusion interval
- Transfusion reaction rate

Cooley Care-WHO Short Guide to the management of Thalassaemia 1987-1990 and TIF 2007

The Hellenic National Programme for the Clinical Management of Thalassaemia

National Registry of Hbpathies (4.506 patients affected by TM, TI, HH and SCD)

- **A network of 32 specialized facilities**
- **Patient records (including blood banking records)**

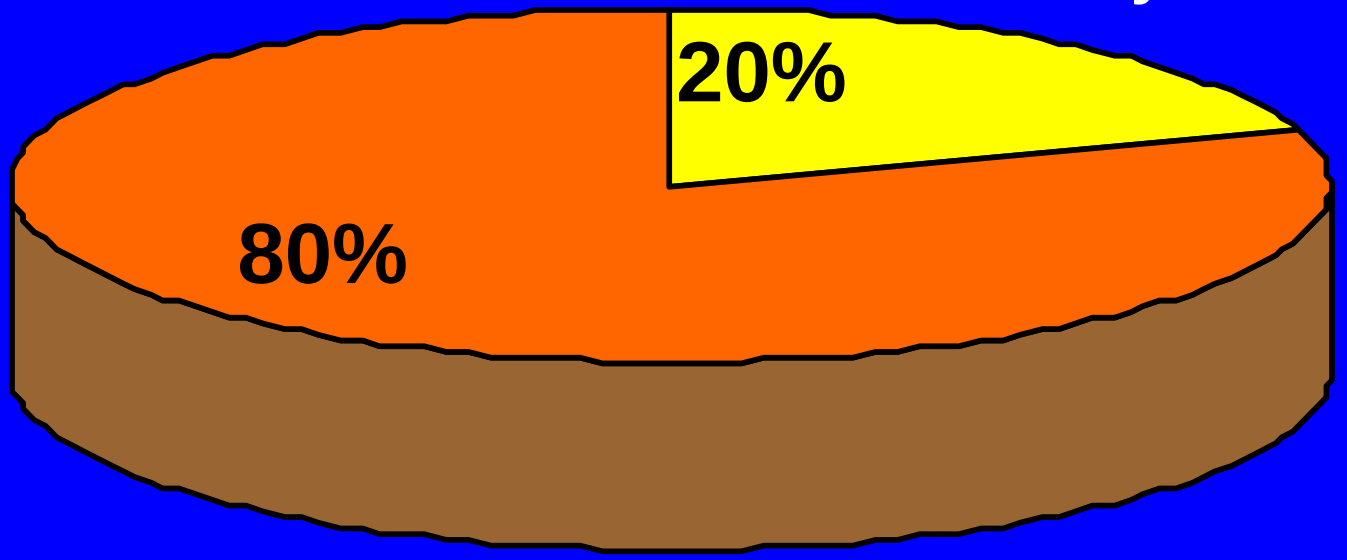
  Model flow and annual summary change
- **Establishing a standardized national database**

The common protocol of transfusion

- **Use of good quality packed RBCs, plasma protein free, leukodepleted and as fresh as possible**
- **Policy of phenocompatible blood**
- **Iron chelation therapy the transfusion of ≃ 20 RBCs units**
- **Reporting adverse events to SKAE**

Hellas 1997 – 2011

National Blood Supply



SKAE report , 2012

Thalassaemic syndromes Hellas, 2011

Demographics and Quality Indicators for transfusion and chelation

• Patients	1, 315 (46% of total)
• Mean age (years)	35±22
• Iron chelation	100% (full compliance varies)
• Average blood consumption	37 units/ patient /year

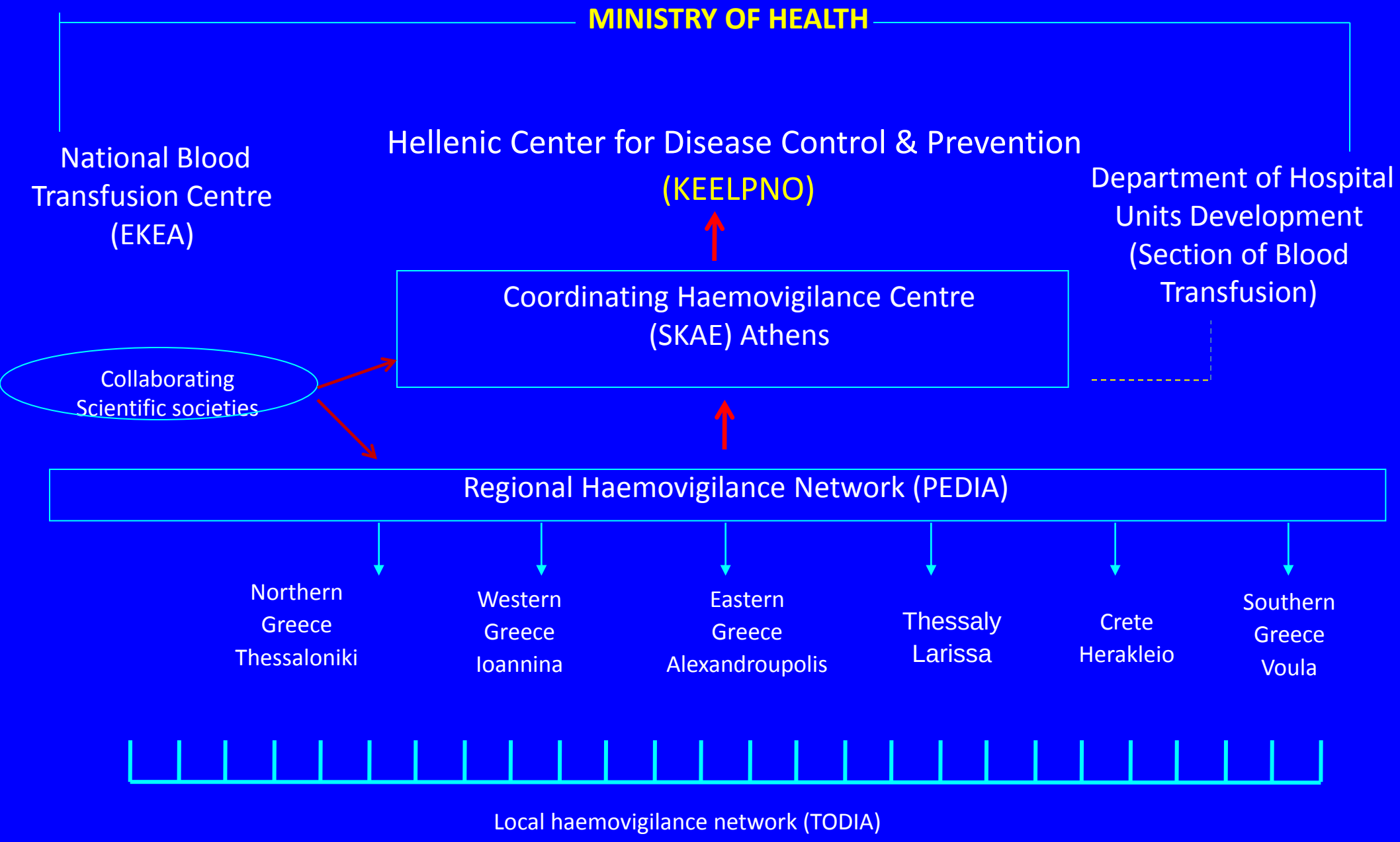
- Screening for irregular antibodies before each transfusion
- Phenocompatibility
  - ABO, CcDEe, Kell 100%
  - Better match policy 28%

- Leukoreduction (filtration)
  - Bedside 60%
  - Pre-storage 40%

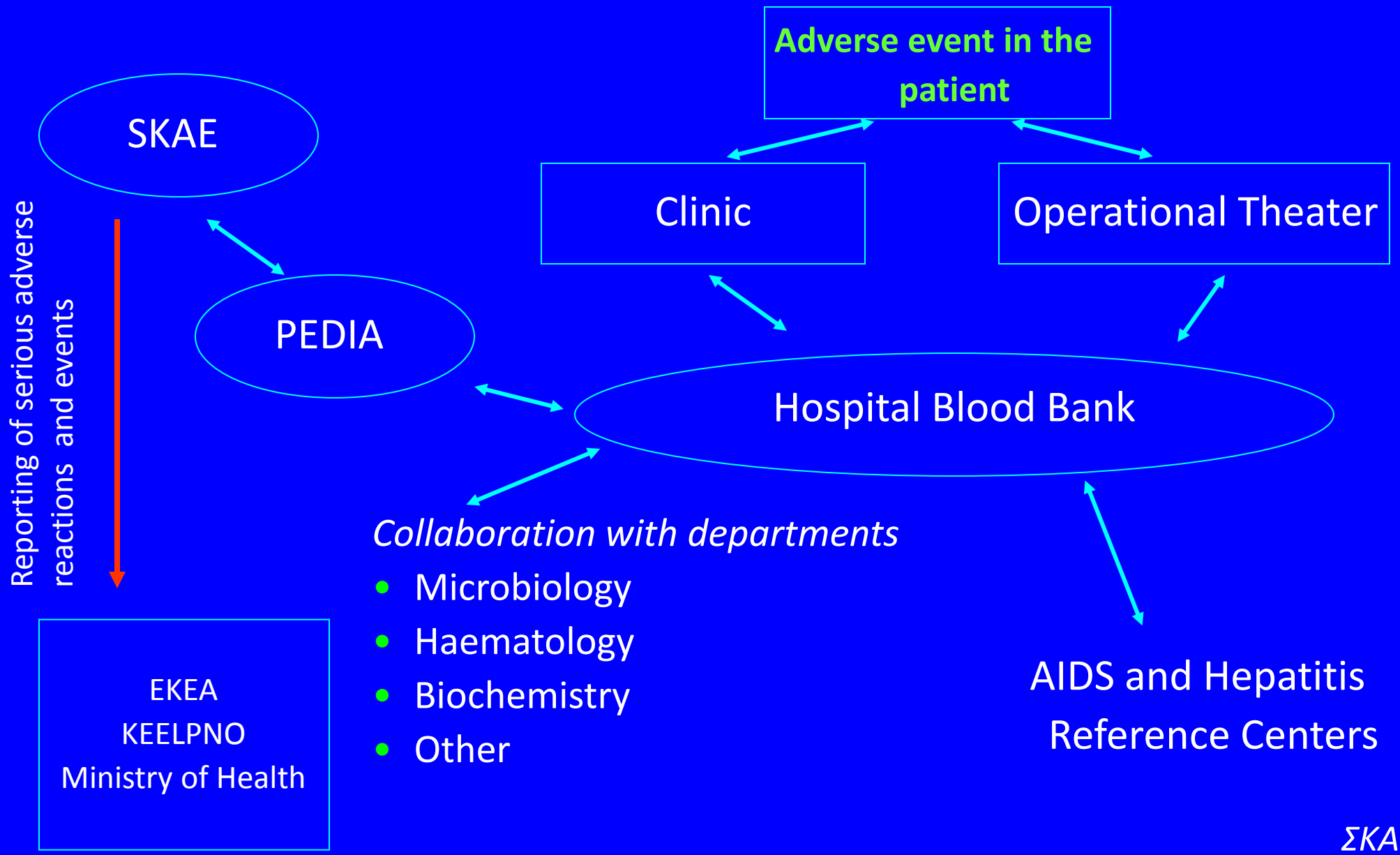
SKAE report, 2012

Haemovigilance data for thalassaemia 1997-2010

SKAE report, 2012


MINISTRY OF HEALTH
National Blood Transfusion Centre (EKEA)
Hellenic Center for Disease Control & Prevention (KEELPNO)
Department of Hospital Units Development (Section of Blood Transfusion)
Coordinating Haemovigilance Centre (SKAE) Athens
Collaborating Scientific societies
Regional Haemovigilance Network (PEDIA)
Northern Greece Thessaloniki
Western Greece Ioannina
Eastern Greece Alexandroupolis
Thessaly Larissa
Crete Herakleio
Southern Greece Voula
Local haemovigilance network (TODIA)

Flow chart of information



ΣΚΑΕ

Total Serious Adverse Reactions, 2006-2011

Incidence 8.3:100.000 components

Deaths

(Grade 4)
n=2 (0.5%)

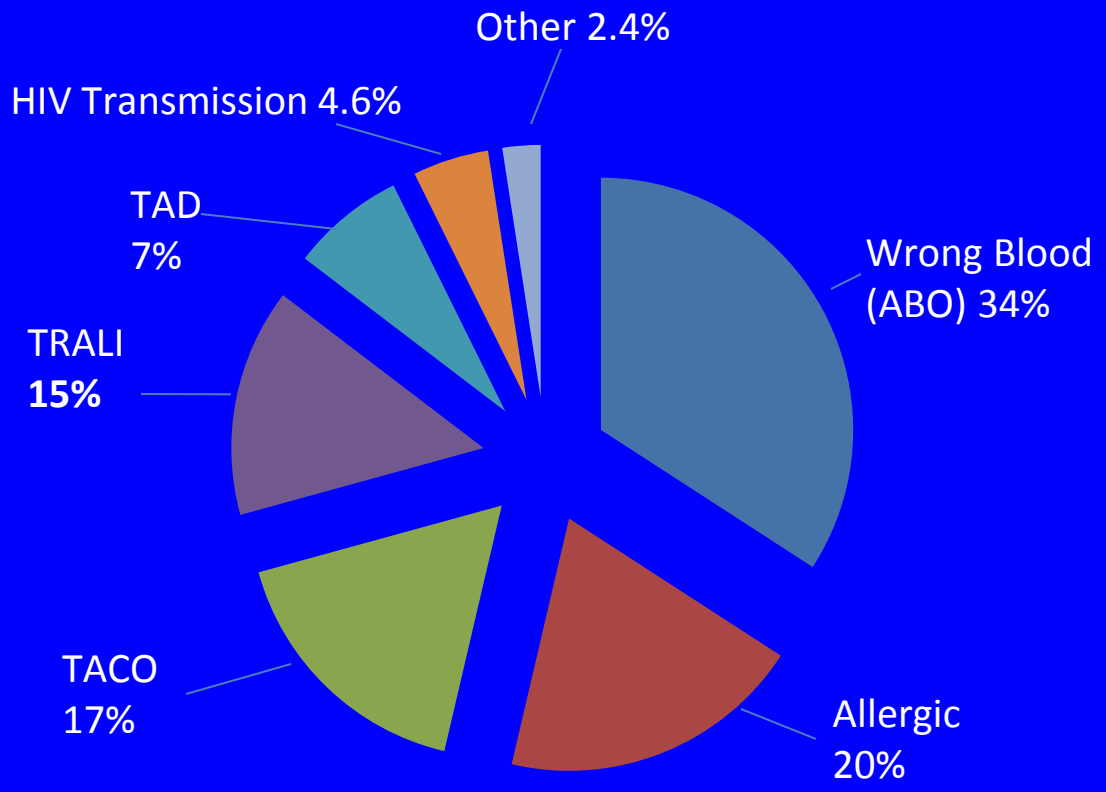
- 1 Hyperhaemolysis in a SCD patient
- 1 TRALI in a surgical case

Life-threatening

(Grade 3)
n= 41 (11%)

Serious

(Grade 2)
n = 330 (88.5%)

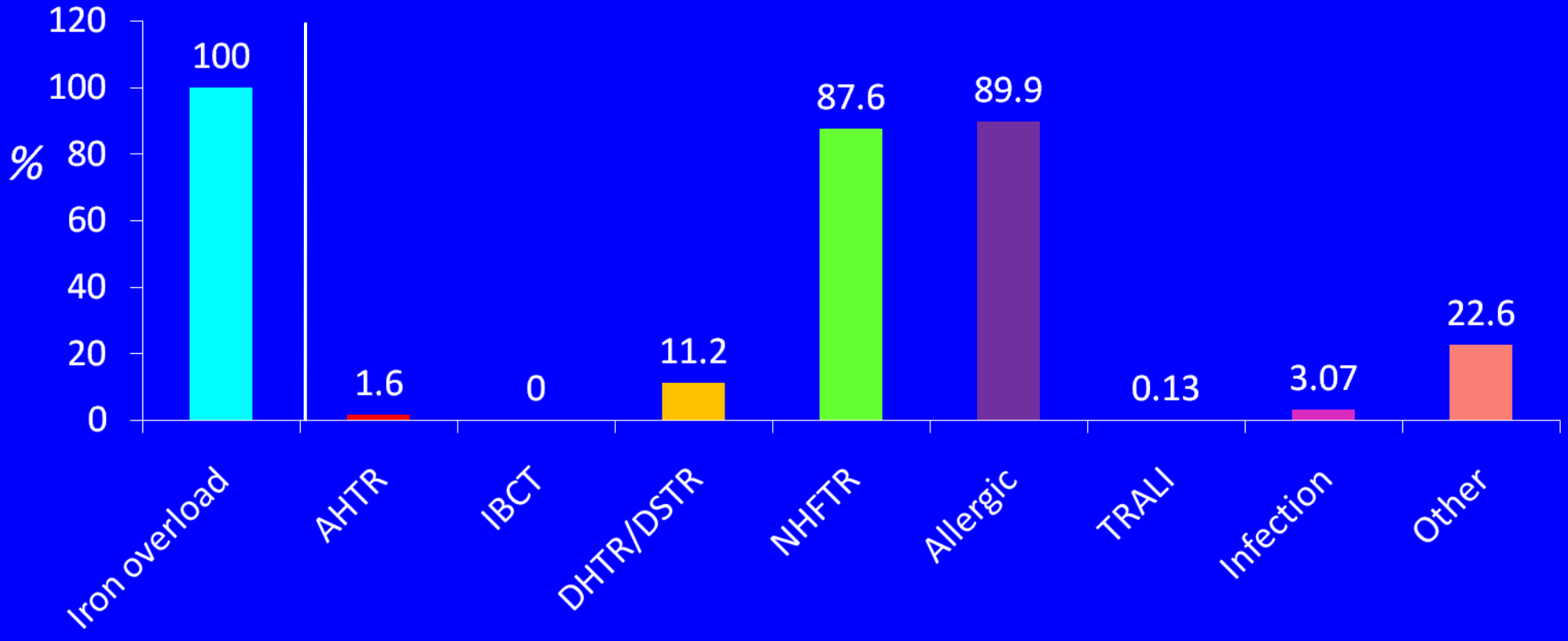


SKAE Report ,Dec. 2012

Adverse reactions in thalassaemia 1997-2010

(n=1,315)

Incidence 21:100.000 RBCs units (ARs without iron overload)
598:100.000 RBCs units (ARs with iron overload)



SKAE Report ,Dec. 2012

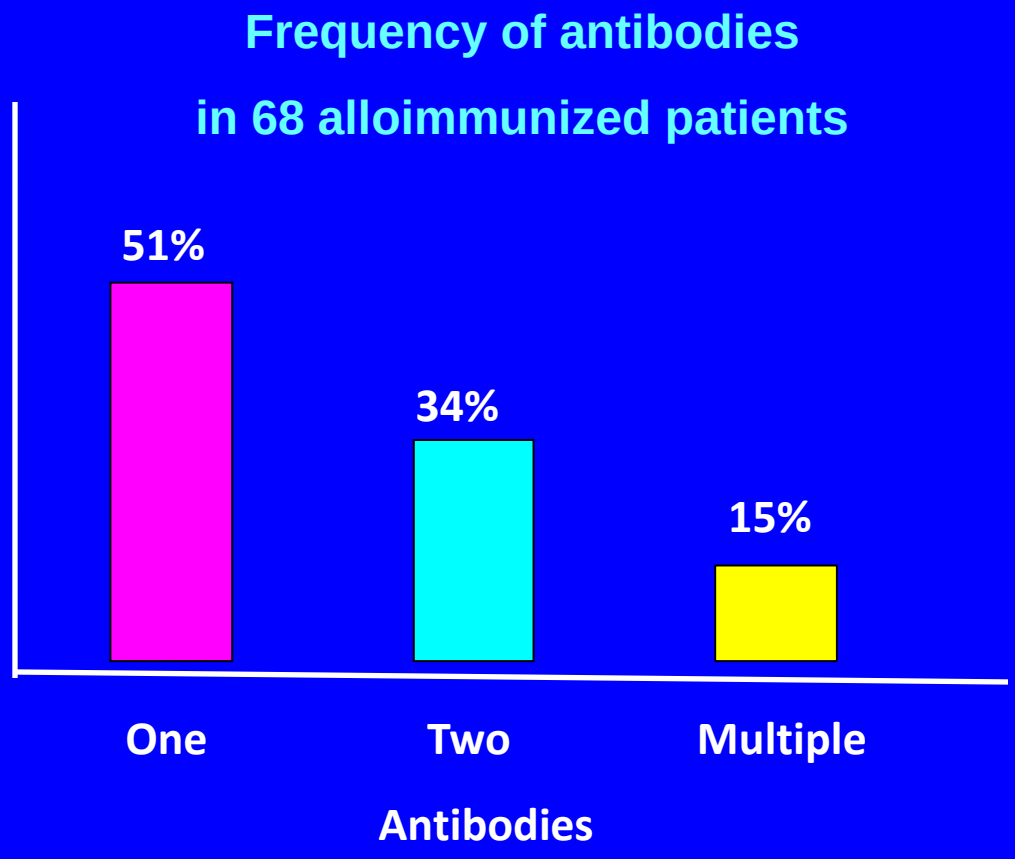
Thalassaemic patients (n=1,315)

Alloimmunization 2.8%

Specificity Rh, JK$^{\alpha}$, Kp$^{\alpha}$, Le$^{\alpha+\beta}$, Fy$^{\alpha+\beta}$ } systems

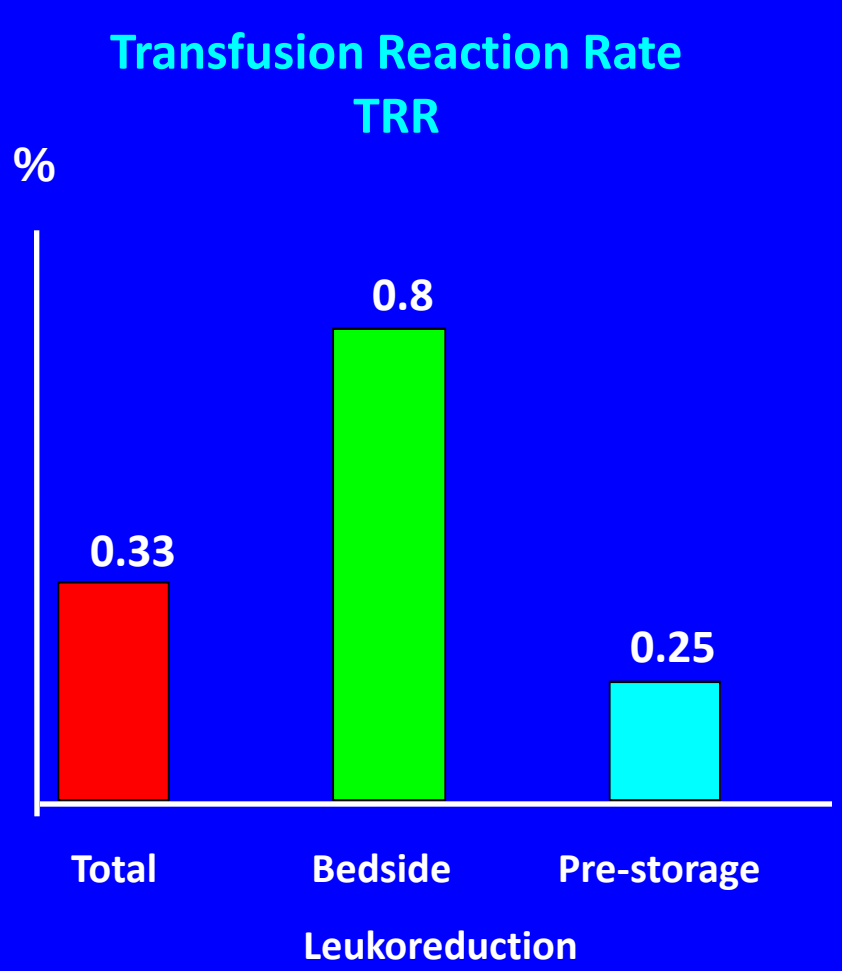
Autoimmunization 1.6%

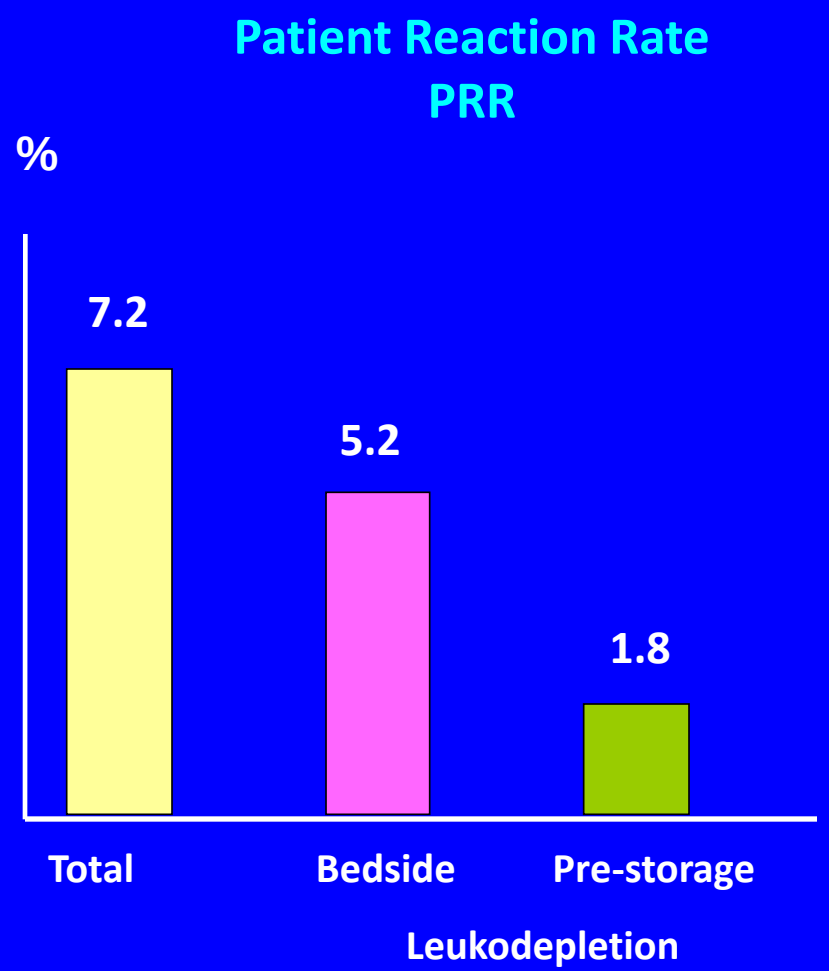
IgG, anti-C_3+, anti-C_4+
DAT ++++



SKAE Report, Dec. 2012

NHFTR in thalassaemic patients





SKAE Report, Dec. 2012

TTIs in Thalassaemia syndromes 1997-2010

Infection	Seroprevalence	Occult	Chronic	Cirrhosis	Carcinoma
HBV	1-2 %	1.3%	5%		
HCV	54 %	?	70% →	20% →	~1%
HIV	0.3 %				
HTLV	0.8 %				
WNV	0.5 %				

Parvo B^{19}		52
CMV		96
EBV		34.5
HSV	%	43.8
ROTA		14.6
Influenza		31.5

Eight died at median time 7.9 years after diagnosis of anti-HCV

Six patients died of septicaemia due to Klebsiella, Yersinia and Proteas

Politis C .Quality Assurance of Transfusion Therapy in Thalassaemia and Sickle cell Anemia . In CRS Press,Quality Assurance in Trans fusion Medicine Vol II, 471-484

SKAE Report , 2012

The protocol of TTIs prevention

Children should be screened for all TTIs and vaccinated against HBV upon diagnosis of thalassaemia

Screening of all patients for HBV, HCV and HIV every six months identifies:

- **Responders to HBV vaccinations**
- **Carriers or chronically infected patients**
- **Those with HBV past infection**
- **All HCV carriers identified through screening should be vaccinated against HAV as there is evidence to support exacerbation of HCV infection in cases super-infected with HAV**
- **All HCV carriers should be monitored for the prevention and early diagnosis of liver cirrhosis and cancer**

Iron overload in thalassaemia

Cause	Mainly
• Blood transfusion	In thalassaemia major
• Gastrointestinal intake	In thalassaemia intemedia

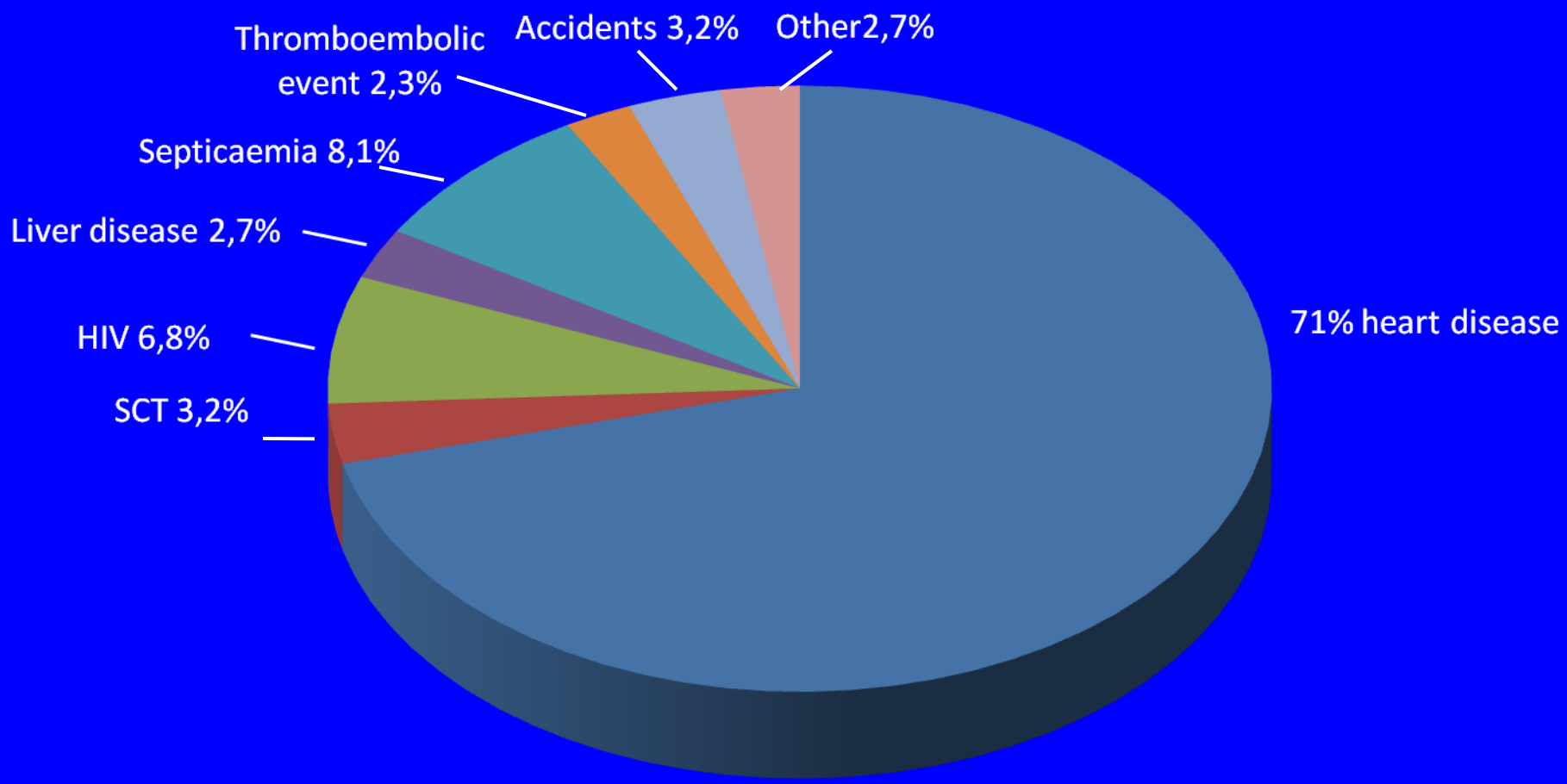
Rate of Fe loading: 200 mg Fe / unit RBC

Recommended transfusion scheme : 100-200 ml RBC / kg /year

(0.32-0.64 mg/kg/day)

In the absence of any mechanism of the body to excrete excess Fe, chelation therapy is essential

Causes of death in Thalassaemic patients, 2000-2008 (n=1044)



Ladis V. et al Survival in a large cohort of Greek patients with transfusion – dependent beta thalassaemia and mortality ratios compared to the general population . Eur. J. Haematology 86 (332-338) 2011

Transfusion Complications in Patients with Haemoglobin Disorders

SHOT

Paula Bolton - Maggs

2010-2011

Disease	Adverse events
Sickle cell disease	32 (70%)
Thalassaemia	14 (30%)
Total	46 (100%)

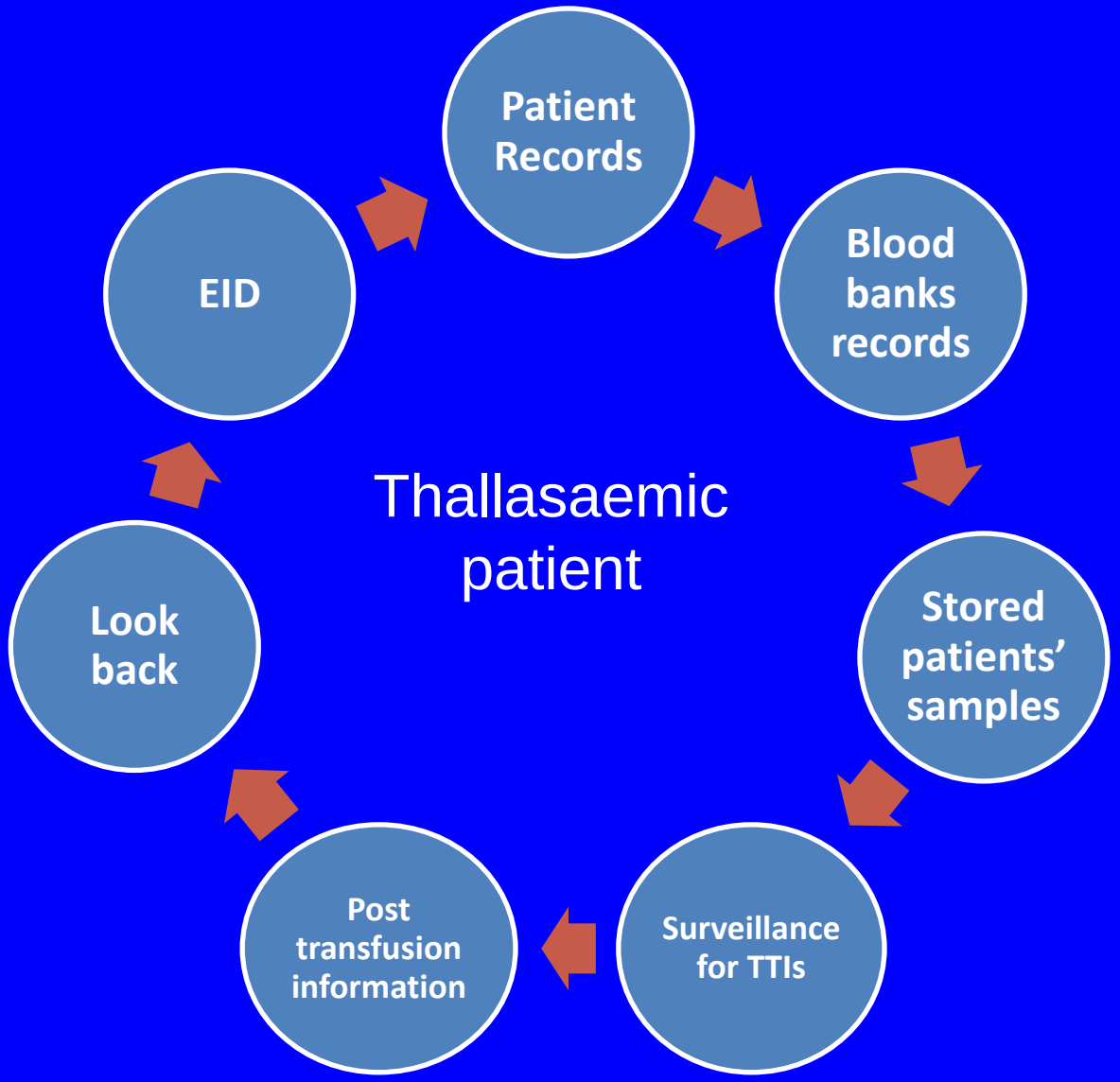
- Failure to provide RBC with appropriate requirements: 27% of cases in SCD
- Alloimmunisation
  - Sickle Cell 9:32 (28%)
  - Thalassaemia 2:14 (14%)
- Acute or haemolytic reactions: 62% of all events in SCD

The outcome of HTR in SCD was 1 death and 5 major morbidity

Commentary: HTRs are unpleasant and dangerous, some are preventable by appropriate choice of RBCs but others are not. Hyperhaemolytic transfusion reaction may be related to macrophage activity

Both HHTR and DHTR must be considered in patients with SCD who present with a ''crisis'' within 14 days of transfusion. Continuous staff training about medical issues in SCD

The contribution of HV to blood safety



Myelodysplastic syndromes MDS

- It is estimated that 10,000-20,000 new cases are diagnosed each year in the USA alone; the incidence in patients over 70 years of age may be as high as 15 cases per 100,000 per year
- Transfused patients requiring relatively large numbers of RBC transfusions present with the adverse reaction of haemosiderosis

This organ dysfunction - if untreated - contributes to increased mortality and morbidity

Aul C. et al Int. J. Hematology 2001, Vol.73 issue 4, (405-410)

Conclusions

- **Haemovigilance data show that:**
  Patients with SCD transfused >200 units are at increased risk of ATRs and alloimmunisation.
  Patients with Thalassaemia major (>500 transfused units) are at increased risk of TTIs and, in the long term, of iron overload

Further improvements are recommended:

- **Phenocompatibility policies**
- **Leukoreduction procedures**
- **RBCs washing**
- **Transfusion-transmitted Klebsiella and Malaria and new emerging threats of transfusion should be further investigated**
- **Transfusion process**
- **Staff education**

Proposals for IHN-ISTARE

- ✓ Collection and analysis of data for ARs/AEs in chronically transfused patients with Haemoglobin Disorders and Myelodysplastic Syndromes may be considered for the ISTARE database
- ✓ The issue of haemosiderosis should be further elaborated
- ✓ Increased surveillance for transfusion-transmissible infections and other adverse reactions as well as post-transfusion information may significantly contribute to the prevention and recurrence of complications and accidents in patients at increased risk of transfusion

Acknowledgements

We are grateful to all transfusionists
and clinicians of the Thalassaemia Units
for their cooperation
Special thanks to SKAE's colleagues

SKAE

WHO

Photo exhibition

London *Trafalgar Square*

14 June 2005

WORLD BLOOD DONNOR DAY

Greek thalassaemic: Winner

Thank you