Hereditary haemochromatosis: implications for donors, products and patients

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Conflict of interest: none

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Agenda

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- Background: policies for HH, blood donation & BC use
- Scientific and ethical questions
- Updating evidence
- Ethical principles for donors and patients: applicability to HH donations for patients?
- Perspectives, challenges

Worldwide policies on HH and blood donation- *Pauwels et al, 2013*

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- *Web-based questionnaire distributed to 44 blood services in 41 countries, responses from 35 BS in 33 countries (80%)*

- **HH carriers/patients accepted as blood donors**

Asymptomatic carriers, normal iron	23	Symptomatic, mainten.	9
Asymptomatic carriers, abnormal iron	19	Symptomatic, depletion	7
Asymptomatic (recovered), mainten.	16	None	11

- Approval of donor physician: 11 / Prescription from treating physician AND approval donor physician: 8
- Higher donation frequency allowed: 8/24
- HH contribution to blood donor pool: <1% (12/24) to 1-5 % (5)

Blood donation from HH patients: scientific and ethical questions

Conry-Cantilena 2001, León de González 2007

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- Blood safe?
  - Possible contamination with siderophilic bacteria, e.g. *Yersinia* sp.
  - Potential higher susceptibility for viral infections?
- Quality of HH blood suitable for blood transfusion?
- Donation voluntary?
  - Phlebotomy as blood donation: possible financial incentive?
  - Necessity of phlebotomy: not qualifying as ‘‘voluntary’’?

Is blood of uncomplicated HH patients safe and effective for blood transfusion?

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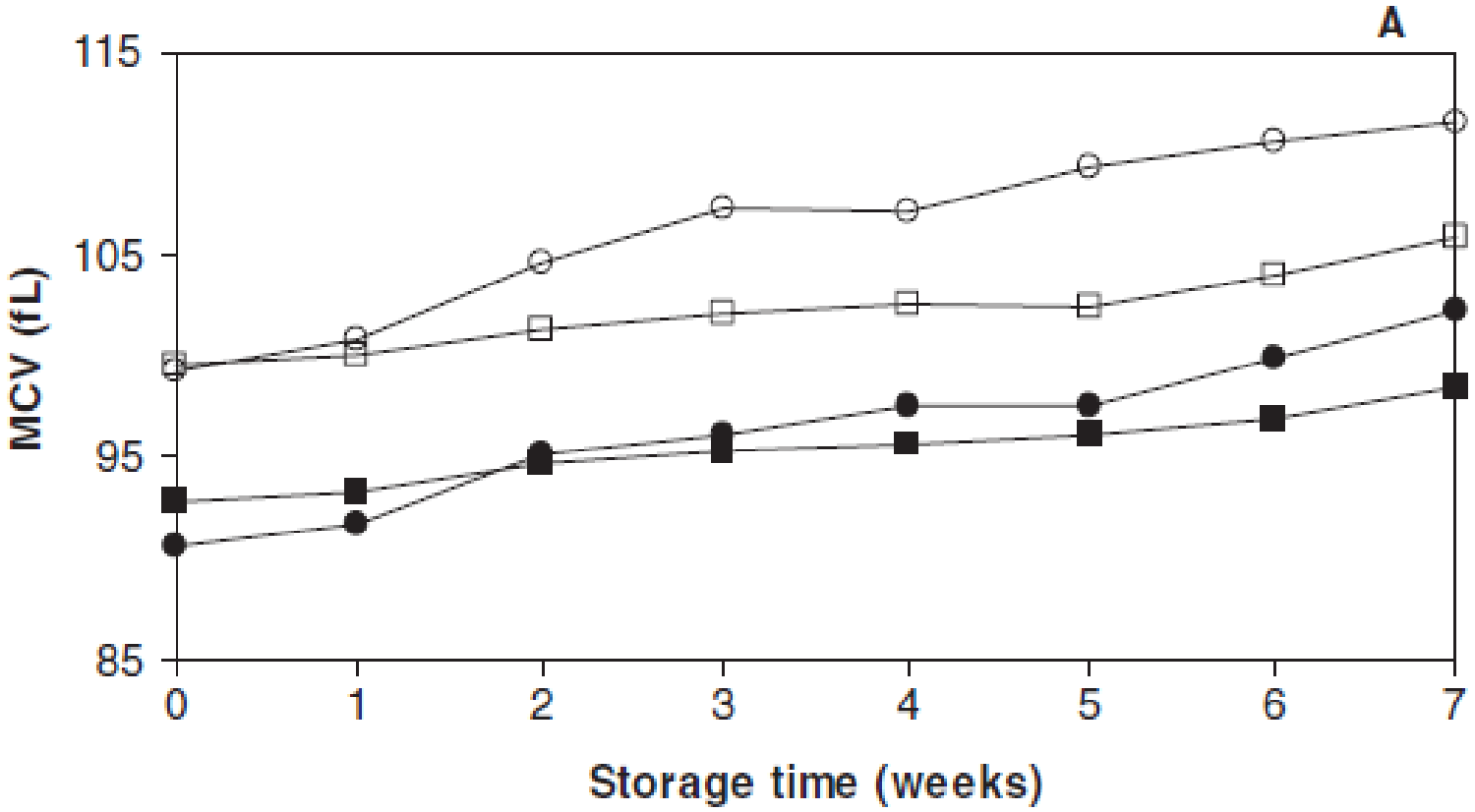
De Buck et al 2012

Cochrane review: 3470 citations, 80 references, 6 observational studies

GRADE level of evidence: low to very low

Study	Population	Assessment
Luten *et al.*,2008, NL	8 HH ,15 BDs	Haematologic & biochemical variables RBCC up to 5O d. storage
Sanchez *et al.*, 2001, USA	52,650 BD including 197 HH	Unreported deferrable risks, TTI screening
Leitman *et al.*, 2003, USA	130 HH	Seroconversions for TTI agents, 27 Mo
Jolivet-Gougeon *et al.*, 2007, FR	236 HH, 303 BDs	Serum Abs against *Yersinia*
Jolivet-Gougeon *et al.*, 2008, FR	26 IO HH, 35 ID HH, 33 controls	Serum antibacterial activity against S. *typhimurium* **Significant decrease for IO HH**
Bullen *et al.*, 1991, USA	5 IO HH, 5 controls	Survival of *Vibrio vulnificus* in blood **Significant increase for HH**

Quality of HH erythrocytes: mean cell volume Luten *et al.*, 2008



Weekly measures of MCV (mean values) during storage of RCCs of different conditions (□ , HWB; ○, HEA; ■ , DWB; and ● , DEA). n = 4 for HWB, HEA, and DEA and n = 11 for DWB.

Morphology of HH erythrocytes:

Pretorius et al 2014

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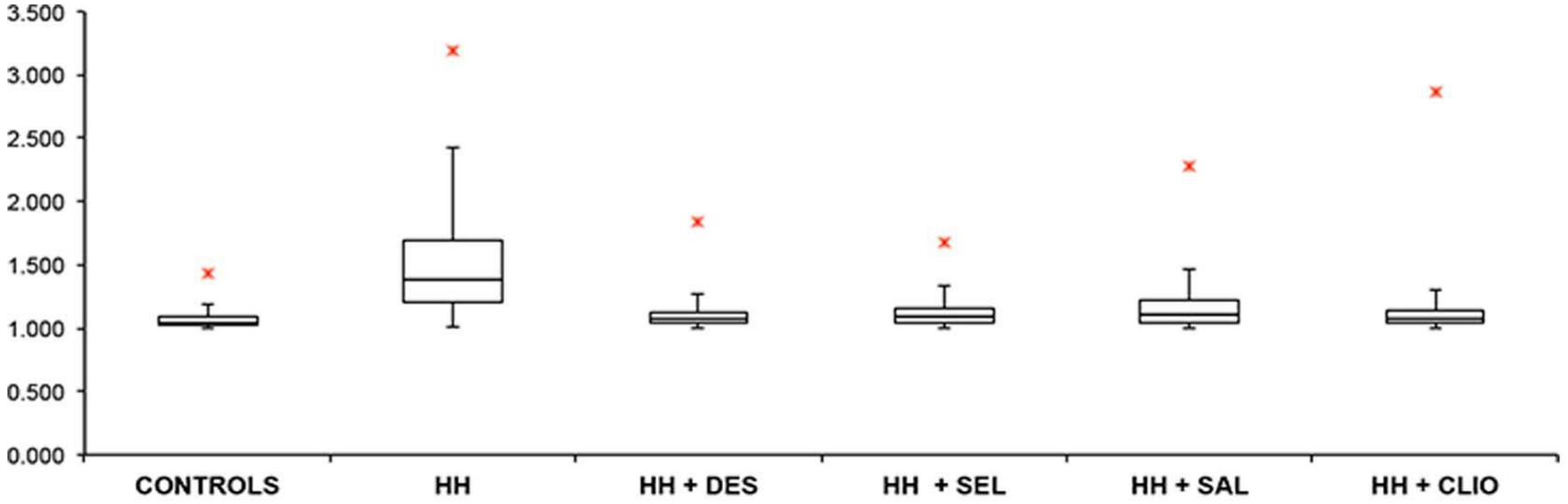
- **Methods**
  - Light microscopy and scanning electron microscopy of RBC from 13 HH patients and 4 patients with hyperferritinemia (HF) vs 17 controls
- **Main findings**
  - HH erythrocytes distorted with a greater axial ratio than controls (close to 1, discoid shape): $p<0.0001$
  - Differences reversed by iron chelators desferal or clioquinol, and free radical trapping agents salicylate or selenite
- **Conclusions**
  - *Aberrant RBC morphology of HH and HF erythrocytes caused, at least in part, by "unliganded iron"?*

Box plot of axial ratios of 20 cells from 17 healthy individuals (n = 340) vs axial ratios of 20 cells from 13 HH individuals (n = 260) with and without chelating and other compounds (n = 260 per compound).

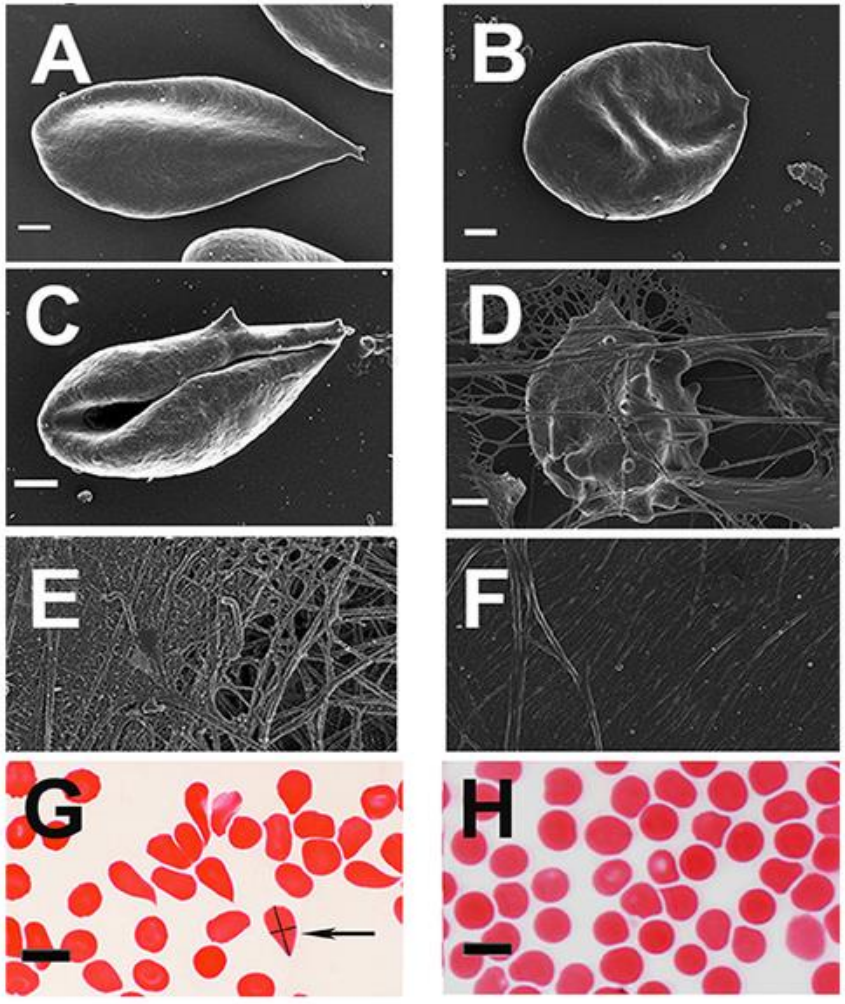
Courtesy E. *Pretorius et al 2014*



	CONTROLS	HH	HH + DES	HH + SEL	HH + SAL	HH + CLIO
Min	1.000	1.002	1.001	1.001	1.000	1.000
Q1	1.024	1.211	1.034	1.044	1.047	1.035
Median	1.049	1.381	1.070	1.087	1.115	1.077
Q3	1.088	1.695	1.131	1.158	1.213	1.143
Max	1.439	3.187	1.833	1.682	2.279	2.866
IQR	0.065	0.484	0.097	0.115	0.166	0.108
SD value	**0.059**	**0.365**	**0.102**	**0.118**	**0.179**	**0.151**

Micrographs from HH and HF individuals.

Courtesy E. *Pretorius et al 2014*



A) RBC from HH individual with high SF; B) RBC from HH individual with low SF; C) elongated RBC from HF individual with high SF; D) WB smear from HH with added thrombin; E) PRP smear from HH with added thrombin; F) PRP smear from HF individual with added thrombin

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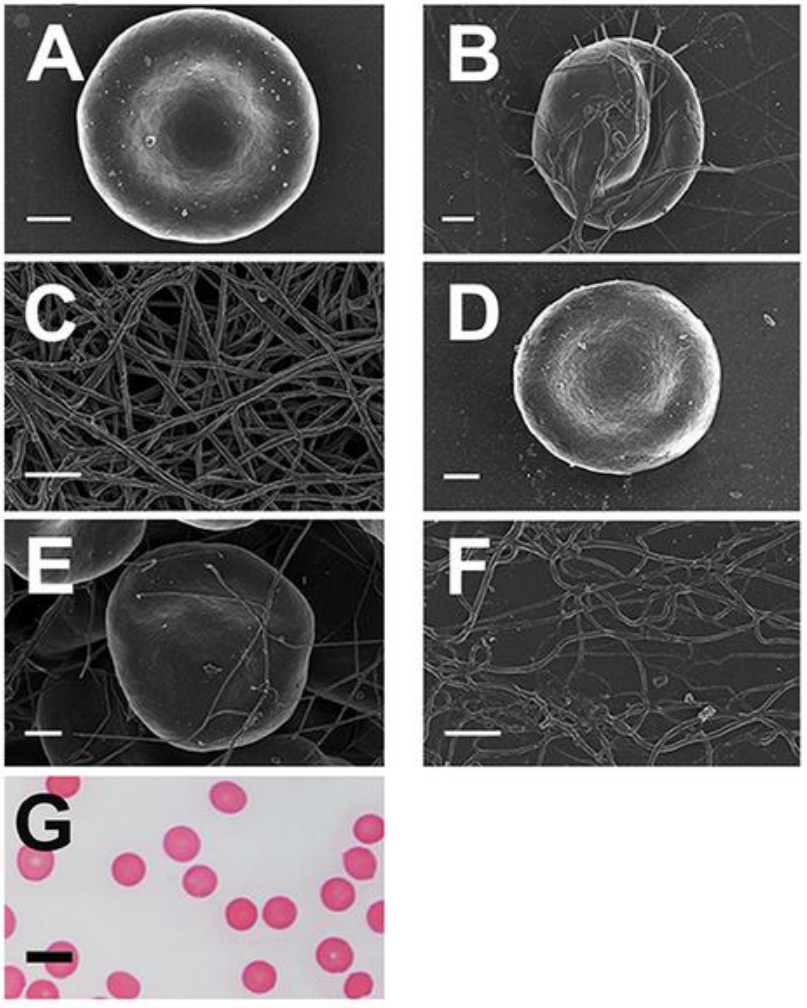
Micrographs of samples from patients with HH with added desferal.

Courtesy E. *Pretorius et al 2014*



A) Whole blood with added 10 mM desferal; B) WB with added thrombin and 10 mM desferal ; C) PRP smear, with added thrombin and 10 mM desferal; D) WB with added 0.5 mM desferal ; E) WB with added thrombin and 0.5 mM desferal; F) PRP smear, with added thrombin and 0.5 mM desferal; G) Light microscopy of WB with 0.5mM desferal

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Validity of the Pretorius's study?

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- HH diagnosis in patient group?
  - 2-4 C282Y/C282Y, 1 H63D/H63D, 3-6 C282Y/H63D…?
  - Iron status: normal SF in 7-10/22?
  - RBC studies in 13/22: selection criteria?
- Blood samples: collection, transport, storage?
- Morphologic studies: which RBC measured?
- Non transferrin-bound iron: not measured
- 30 µM $FeCl_3$: not physiological condition.

➢ **Proper controlled study needed to investigate increased MCV in HH patients.**

Mutations in the HFE gene: potential advantage? Hermine et al 2015

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- Frequency of mutations in HFE gene (H63D, C282Y,…*)* in French elite athletes (energetic sport: 129; non energetic sport: 41) vs controls matched for age, gender and geographical origin (219).

  - Athletes: 41%
  - International podium group: 80.4%
  - Controls: 27%

Impact of HFE mutation on Hb concentration in athletes & controls. Hermine et al 2015

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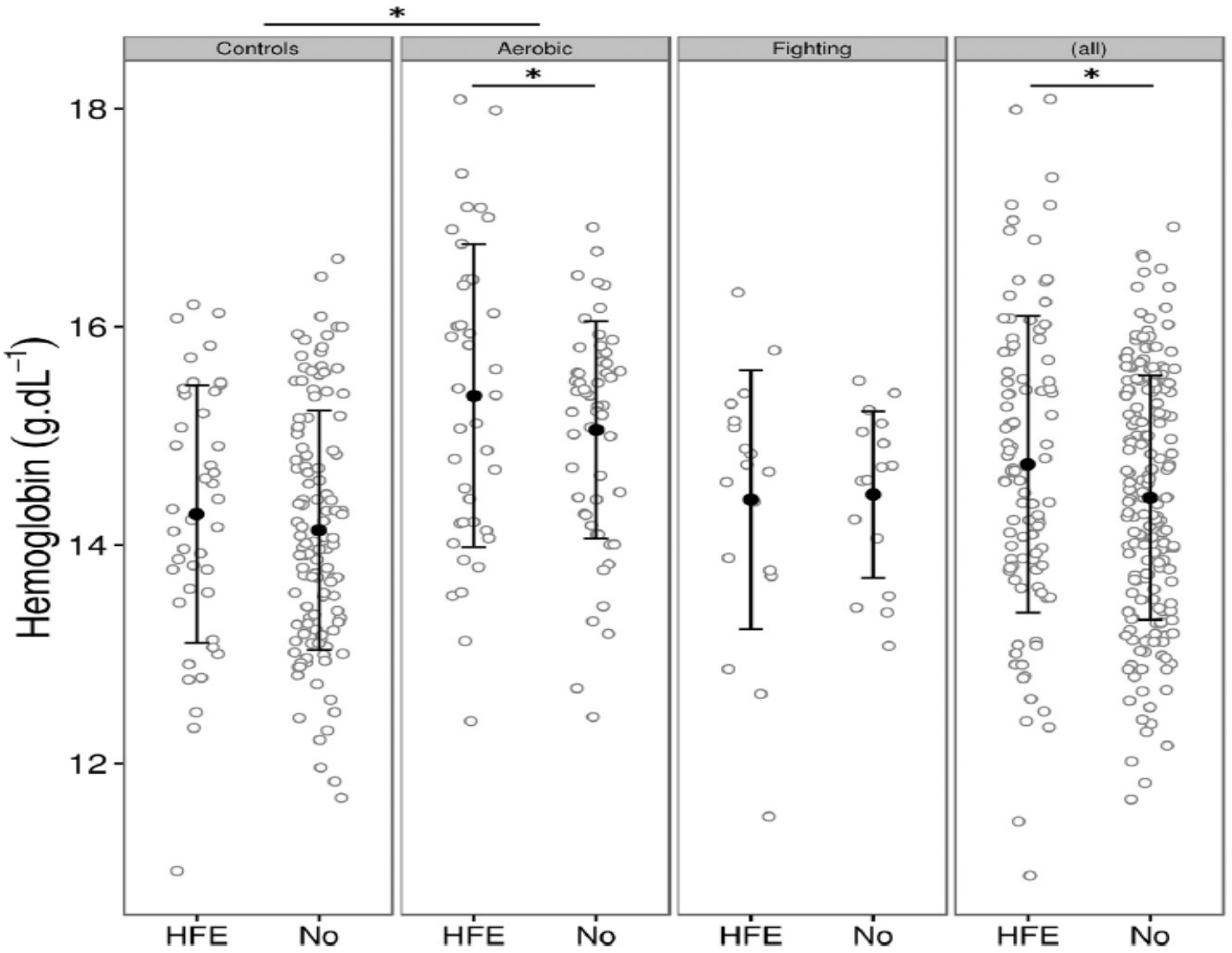

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Ethical principles for D & R of human bodily materials

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Well acknowledged **four principles of biomedical ethics** to protect donors' and patients' safety :

- Autonomy
- Non-maleficence
- Beneficence
- Justice

Human dignity

Ethical principles for donors
1. Autonomy

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- ***Respecting the decision-making capacities*** of autonomous donors: reasoned informed choices about their donations.
- Respect for autonomy involves
  - ***Information*** (risks to donor) and ***consent*** before donation.
  - ***No undue influence or pressure****: medical decision of phlebotomy impacting HH donor autonomy?*
- ***Donor's autonomy could impact patient's safety****: HH donor led to hide personal health information and prevent accurate risk assessment?*

Ethical principles for donors
2. Beneficence

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- Considering the balancing of benefits of blood donation against its risks and costs
- Not applicable to blood donors:
  - donor submitted to a medical procedure for which he/she will ***not derive any direct medical benefit***
  - any adverse reaction caused by the collection procedure ***will not be offset by a benefit*** to donor.

- **HH patients: donors or patients?**

Ethical principles for donors
3. Non-maleficence

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- ***Avoiding*** the causation of ***harm*** to the donor

- Compliance with **professional standards**
- Continuous improvement of knowledge and **prevention of adverse reactions** to blood and blood component collections
- Avoidance of unnecessary donor selection

- **HH patients: donors or patients?**

Ethical principles for donors
4. Justice

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- ***Avoiding*** the "burden of donation" being shifted to underprivileged populations
- Remuneration of donors: risk that those who are most likely to donate belong to ***lower socio-economic groups*** and be the least likely to benefit from blood products if they needed blood.

- **Higher donation frequency for HH carriers/patients?**

Ethical principles for patients
1. Autonomy

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- Right for autonomous patients to determine what they ***will (and will not) be done with their own person*** ***(t***o choose or refuse any proposed medical treatment).
- Respect for autonomy involves
  - ***Information,*** professional and truthful, not withholding information from patient and/or family, and not advocating for one practice that might not be in the patient's best interest.
  - ***Consent*** before decision of transfusion or no-transfusion.

- **Should recipients be informed when blood from HH?**

Ethical principles for patients
2. Beneficence

- Considering the balancing of benefits of blood transfusion against its risks and costs
- The healthcare professional should act in a way that benefits the patient.
- Ethical expression of the ***physician's commitment*** to do or promote ***only good things for patients***.
- **HH RBC morphological changes? Impact on recipients?**

Ethical principles for patients
3. Non-maleficence

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- ***Avoiding*** unnecessary or unreasonable harm to patients

- Compliance with ***professional standards***
- Not treating a patient without a **documented medical indication** based on the best available evidence
- Harm should not be disproportionate to the benefits of treatment.

- **HH blood as safe as blood from normal donors?**
  - **Possible higher bacterial risk for PC, FFP?**
  - **Behaviour of HH RBC in recipients?**

Ethical principles for patients
4. Justice

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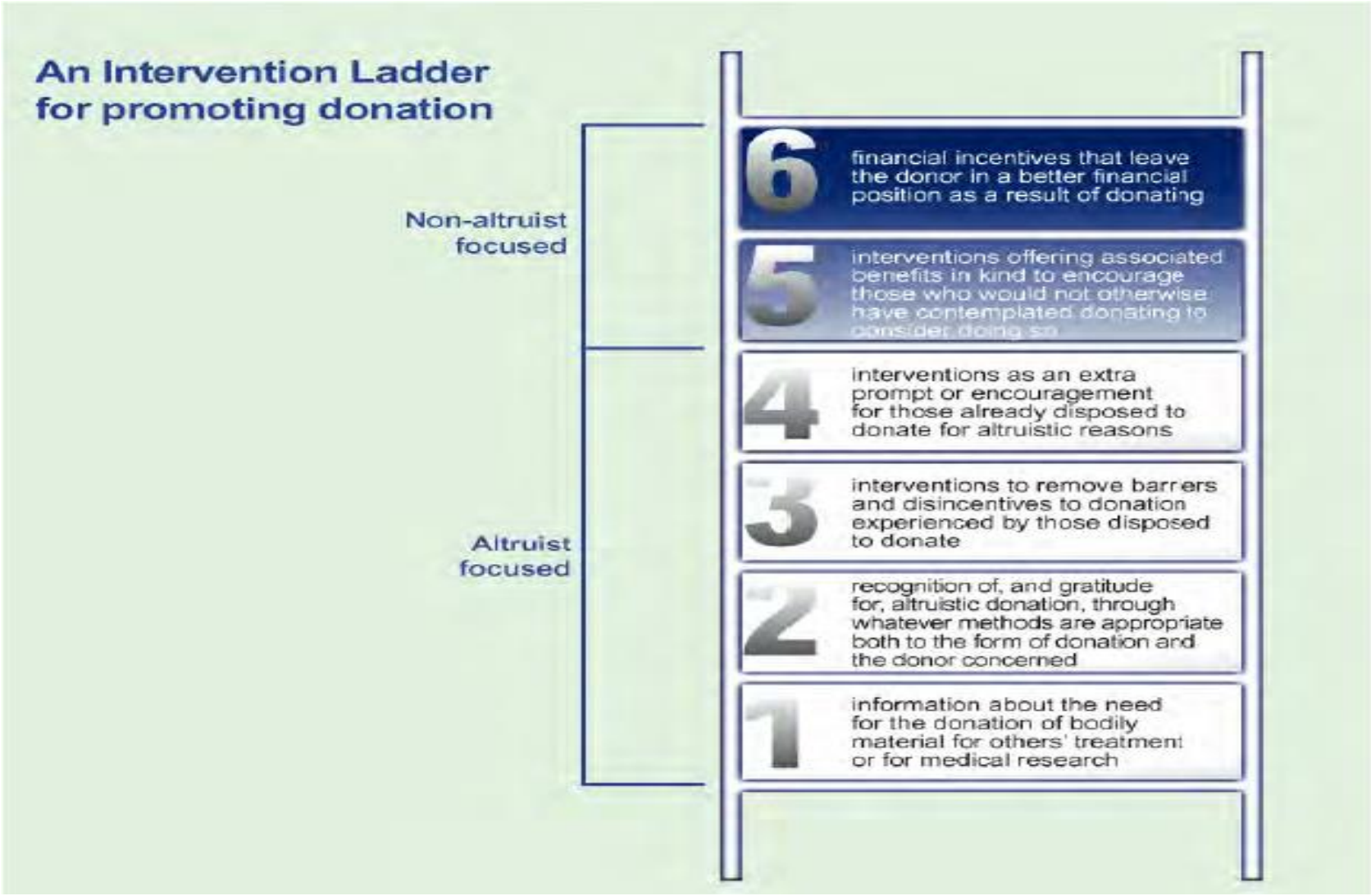
- Patients should be ***treated equally*** for the same healthcare condition.

- Medical decisions: based on the ***best available evidence***
- ***Equitable access*** to treatments: ensured for patients and adapted to the local healthcare situation.
- Discrimination according to factors such as patients' resources, ethnicity: avoided.

- **HH RBC equivalent to RBC from normal donors?**

Nuffield Council on Bioethics *intervention ladder:* a tool for considering ethical acceptability of donor incentives



HH patients vs donors: an ethical dilemma?

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- **Donor's ethical principles in conflict with patient's ones?**
  - Autonomy and beneficence of HH donors
  - conflicting with autonomy, beneficence, non maleficence and justice applying to transfused patients?

- **Renewed ethical reflexion required**
  - Weighing relative acceptability for each of 4 ethical principles to protect transfused patients and HH patients/donors?

Perspectives, challenges

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- **Available evidence**
  - Platelets, plasma from HH patients: higher bacterial risk ?
  - RBC: increased MCV, what beyond?
- **Ethical issues:**
  - HH patients: donors or patients?
  - Recipients of HH RBC: to be informed?

➢ **For the benefit of patients shouldn't we consider:**

- ❑ Focus from **haemovigilance** on PC, FFP from HH patients?
- ❑ Assessing **RBC changes in HH**, in a **controlled study**?
- ❑ Depending on results
  - ❑ Limiting HH donations to **before iron overload**?
  - ❑ Adding HH with iron overload as CI to blood donation?

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Thank you for your attention,
Your questions, comments