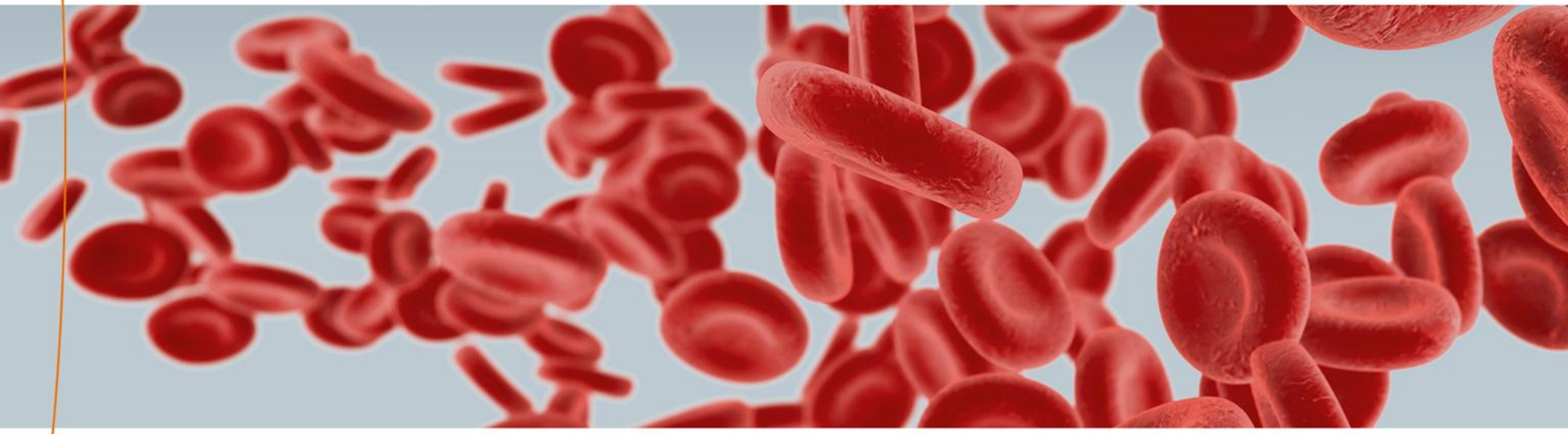
Alternatives to transfusion: caveats



Paul Strengers
Sanquin, Amsterdam
XVth Seminar of IHN, February 20-22, 2013
Brussels, Belgium

RESEARCH | DIAGNOSTICS | PHARMACEUTICALS

Demands for medical alternatives to blood transfusion

- Jehovah's Witnesses
- Surgeons
- Anesthetists
- Hematologists
- Hospital managers
- Network for Advancement of Transfusion Alternatives (NATA)

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Reasons for demand for medical alternatives to blood transfusion

- Risks on transfusion transmittable infections
- Risks on higher incidence of infections
- Risks on immune modulation
- Risks on decreased patient survival
- Safety of blood transfusion
- Questions on the efficacy of blood transfusion
- Lack of sufficient supply
- Costs

Costs

In the Netherlands, the incremental cost-effectiveness ratio of

- Triplex NAT (HBV,HCV,HIV), in addition to serologic testing : € 5.20 million per quality-adjusted life-years (QALY)
- Anti-HTLV-I/II : € 45.2 million / QALY
- HAV NAT : € 18.6 million /QALY

Borket-Raven BA et all. Cost-effectiveness of additional blood screening tests in the Netherlands. Transfusion 2012;52:478-488.

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Medical alternatives to blood transfusion

Surgical devices to minimize blood loss

- laser surgery
- electrocautery
- electrosurgery, etc.

Techniques and devices to control bleeding and shock

- controlled hypotension
- shock position
- prompt surgery
- ice packs, etc.

Surgical and anesthetic techniques to limit blood loss

- hypotensive anesthesia
- induced hypotermia
- acute normovolemic hemodilution
- hypervolemic hemodilution
- intraoperative / postoperative blood salvage
- arterial embolization, etc.

Devices and techniques that limit iatrogenic blood loss

- essenial tests only
- microsampling, etc.

Medicinal alternatives to blood transfusion

Volume expanders

- *Crystalloids*
  - Ringer;s lactate
  - Normal saline
  - Hypertonic saline
- *Colloids*
  - Pentastarch/ Hetastarch
  - Gelatin
  - Dextran

Hemostatic agents for bleeding / clotting

- Aprotinin
- Conjugated estrogens
- Vasopressin
- Recombinant factor VIIa

Therapeutic agents for managing anemia

- Hemoglobin solutions
- Perfluorocarbon-based oxygen carriers
- Hematinics (iron, folic acid, vitamin B12)
- Erythrocytes stimulating agents (ESAs)

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What about … ?

- Risks
- Safety
- Efficacy
- Supply
- Costs

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Examples

- Hemoglobin-based oxygen carriers
- Erytrocytes stimulating agents (ESAs)
- Plasma substitutes for albumin

Therapeutic agents for managing anemia

- Hemoglobin solutions
- Perfluorocarbon-based oxygen carriers
- Hematinics (iron, folic acid, vitamin B12)
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Hemoglobin-based oxygen carriers

- Surface-modified haemoglobin
- Intramolecular cross-linked haemoglobin
- Liposome-encapsulated haemoglobin

- Indications:
  - situations where red cells are unavailable: military actions
  - universal compatibility with all blood types
  - freedom from transmission of TTI
  - prolonged storage under extreme circumstances

Haemoglobin solutions

Biopure

Northfields

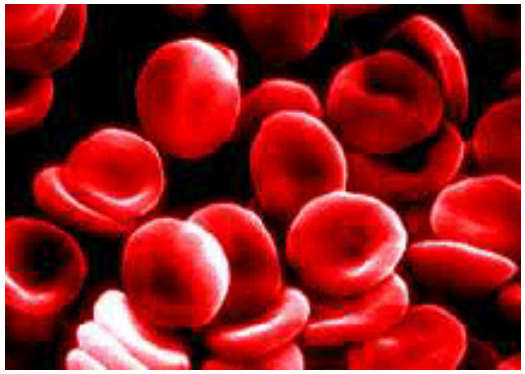
Sangart

Perfluorocarbons

Alliance

Oxycyte

Perftoran



Cultured red cells

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Biopure

- Medicine from food grade cows ???
- Claim complete prion removal
- Licensed in South Africa
- Licensed as a veterinary medicine.
- Used in 1000 + patients in elective surgery
- Further clinical trials in US suspended;
- Under investigation by SEC

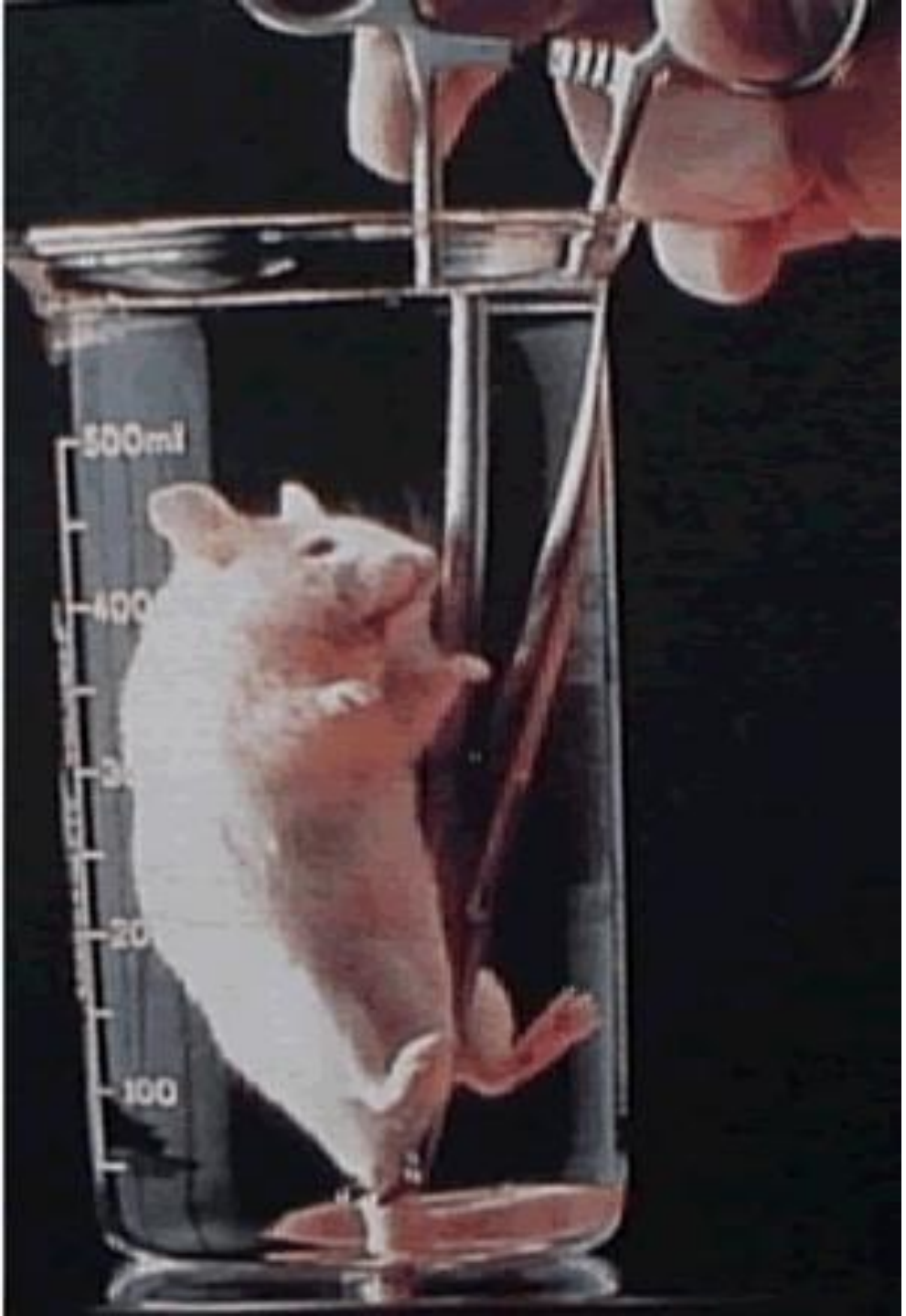
Hemoglobin-based oxygen carriers

Adverse events:

- All: vasoconstriction, reduction of cardiac output, jaundice, myocardial infarction, stroke, acute renal insufficiency, increased arterial blood pressure, methemoglobinemia, increased liver enzymes, and deaths. Gastrointestinal discomfort can occur.
- Diaspirin cross-linked hemoglobin: increased mortality
- O-raffinose cross-linked hemoglobin: cardiac problems

Traynor K. Am J Health Syst Pharm 2008; 65(12):1110-1112; Chang TM. Crit Care Clin 2009;25(2):373-82.

Freilich et al.J.Trauma 2009;66(2):365-76.



Perfluoro-carbons

100 mls = 1 to 4 units of red cells

Can be used to very low haematocrits

Oxygent™ - Perflubron Emulsion

Oxygen Delivery System

Phase III study terminated due to possible increase of strokes

Alliance

- **Produced and licensed in Russia since 1997**

- **January, 21, 2005 : Lectures on clinical application of Perftoran in infusion-transfusion therapy in the Centre of Science of Surgery of Russian Academy of Medical Science, Moscow**

- **Main adverse events: hypotension; pulmonary complications (1% in randomized trial); allergic reactions in particular after inappropriate warming**

E. Zhiburt, personal communication

Cohn CS, Cushing MM Crit care Clin 2009;25(2):399-414

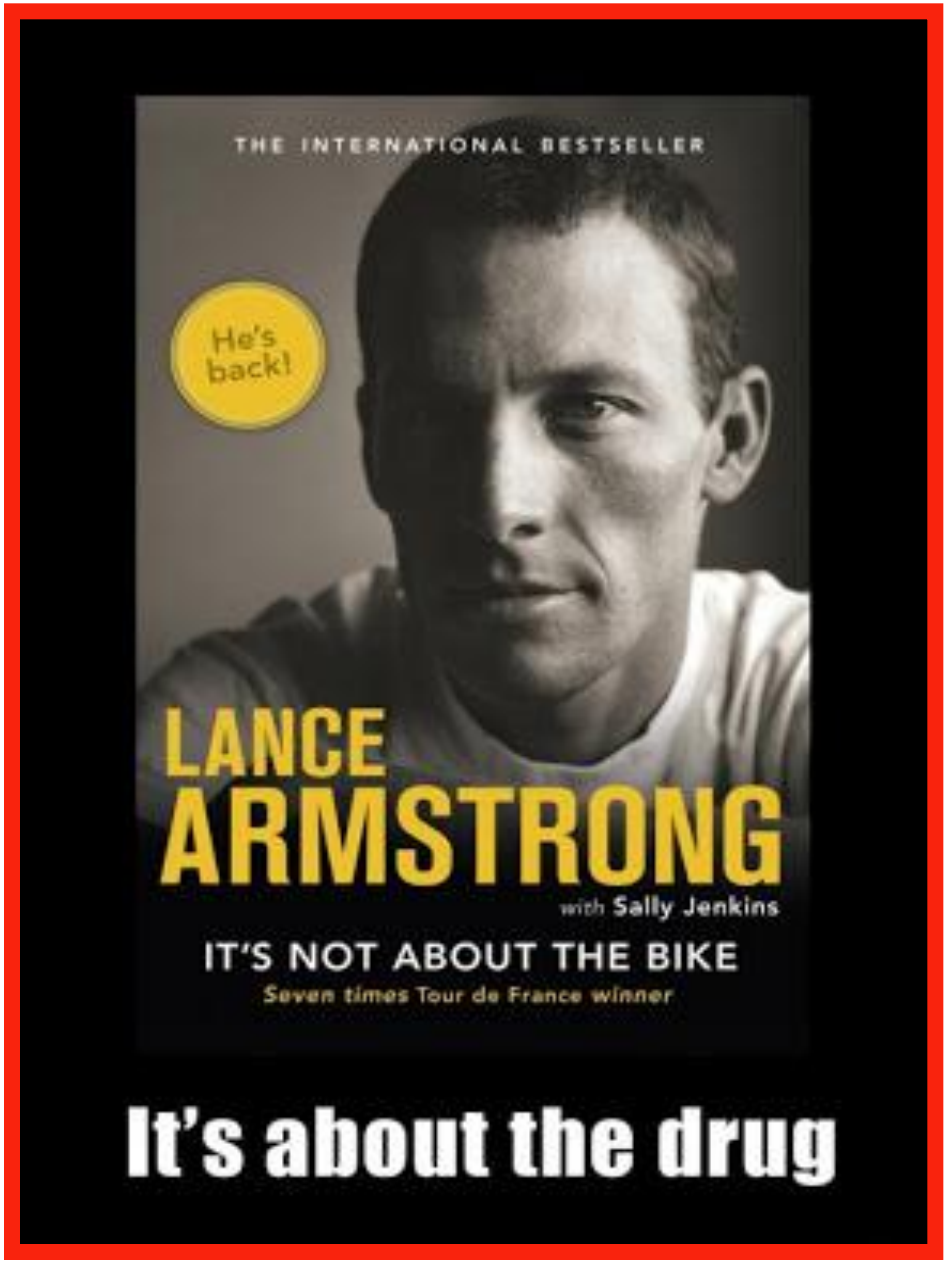
Perfluorocarbons

- Adverse events:
  - complement activation
  - reduced platelet function
- Perfluoro-octyl bromide:
  - clinical trial has stopped: increased incidence of stroke in cardiac by-pass patients
- New perfluorocarbon emulsion:
  - increased blood viscosity

Jouan-Hureaux et al. Transfusion 2006;46(11):1892-8.

Erytrocytes stimulating agents (ESAs)

- Recombinant human erythropoietin (rHuEPO)
  - Epoetin alfa (t½: 8 hrs)
  - Epoetin beta (t½: 8 hrs)
- Darbepoetin alfa (t½: 49 hrs)


THE INTERNATIONAL BESTSELLER
He's back!
LANCE
ARMSTRONG
with Sally Jenkins
IT'S NOT ABOUT THE BIKE
Seven times Tour de France winner
It's about the drug

Erytrocytes stimulating agents (ESAs)

Indications:

- Correction of anemia in chronic renal disease
- Correction of anemia related to cancer or cytotoxic drugs
- Chronic heart failure
- Acute myocardial infraction
- Anemia after cardiac transplantation

Experimental:

- Stroke; diabetes; reduction of red cell transfusions; critically ill patients

Not approved:

- Symptoms of anemia (in surgical patients; patients with HIV infection; fatigue in patients with cancer)

Adverse events of ESAs

- Common: Injection site reactions; purities; influenza-like symptoms; peripheral edema; non-specific rashes; dyspnoe; upper respiratory infections; hypertension; seizures; procedural hypertension; nasopharyngitis; muscle spasms; pyrexia; hypokalemia; hypophosatamia.
- Increased risk: Cardiovascular/ thromboembolic events (partly due to effects of increased Hb on viscosity / platelet-erythrocytes interactions or direct effects of erythropoietin on platelets or vascular endothelial cells); pure red cells aplasia.

Haljan G et al. Stroke 20; 40 (8): 2769–75; Carrera F et al. Dial Transplant 2010; 25(12): 4009–17; Arroliga AC et al. Crit Care Med 2009; 37(4): 1299–307; Ludwig H et al. J Clin Oncol 2009; 27(17): 2838–47; Stowell CP at al. Spine (Phila Pa 1976) 2009; 34(23): 2479–85; Schrijvers D, et al. Ann Oncol 2010; 21(Suppl. 5): v244–7.

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Safety of EPO

Analysis of 12 randomized controlled trials

- rHuEPO vs placebo
- Anemic patients with cancer
- 1.55 times increased risk on thromboembolic events
- 1.25 times increased risk on hypertension

Bokemeyer et al. Eur J Cancer 2004;40(15):2201-16

Updated review of 57 trials and 9,35 patients with cancer

- Significant reduction of red cell transfusions
- Increased risk on thromboembolic events

Bohlius et al. J Natl Cancer Inst 2006;98(10):708-14

Safety of EPO

- In 5-10% of patients: hypo-responsiveness

Johnson et al. Nephrology 2007;12:321-30

- Prospective randomized placebo-controlled trial:
  - n = 1460 surgical or trauma patients
  - dose EPO 40,000 U or placebo
  - weekly for max. 3 weeks
  - follow up 140 days

No reduction of incidence of red cell transfusions

Thrombotic vascular events: 16.5% vs 11.5%

Thrombotic vascular events in pts without heparin: 20.3% vs 12.8%

Thrombotic vascular events in pts with 3 doses EPO: 22.8% vs 16.1%

Corwin et al. N Engl J Med 2007;357:965-76

Safety of EPO

Concerns:

- Neurovascular diseases: risk on cerebral ischemia due to increased blood viscosity

- potential progression of cancer due to blocking of tumor cell apoptosis, stimulating chemotaxis, increased metastatic disease, assisting in tumor genesis

- Meta-analysis (12 randomized controlled studies in 2297 patients)

epoetin-beta: no detrimental effect on survival or tumor progression when given at Hb concentrations of up to 11 g/dl. Unfortunately, the Hb response to epoetin-alfa is unpredictable.

In cancer-induced anemia, ESAs should be given at the lowest possible dose to prevent the need for erythrocyte transfusions.

Aapro M, Osterwalder B, Scherhag A, Burger HU. Br J Cancer 2009; 101(12): 1961–71.

Crouch Z, DeSantis ER. Am J Health Syst Pharm 2009; 66(13): 1180–5.

Safety of EPO

FDA Public Health Advisory, 2007

- Based 4 studies in cancer patients
- Unapproved dosage regimen and unapproved patient population

- Higher incidence of death
- Increased rate of tumor growth; when EPO was given to maintain Hb-level > 12g/dl
- Higher chance of death without reduction of blood use when EPO was given in cancer patients with anemia not receiving chemotherapy
- Higher chance of blood clots in patients scheduled for major surgery

Plasma substitutes for albumin

- Hydroxy ethyl starches
- Dextrans
- Gelatins

- All increased risks on:
  - anaphylactic reactions:
    - hydroxyl ethyl starch: 4.51 per 10*5 infusions
    - dextran: 2.32 per 10*5 infusions
    - gelatine: 12.4 per 10*5 infusions

Barron et al. Arch Surg 2004; 139(1): 552-63

- renal impairment

Davidson Eur J Anaesthesiol 2006;23(9):721-38

Plasma substitutes for albumin

- Dextrans - The incidence of acute renal insufficiency associated with dextrans is estimated to be 4.3%in dehydrated patients.

Farrugia A. J Clin Pharmacol 2011; 51(3): 292–300.

- Hydroxyethyl starch (HES) is strongly associated with acute kidney damage and a need for renal replacement therapy.

Farrugia A. J Clin Pharmacol 2011; 51(3): 292–300.
Davidson IJ. Crit Care Med 2009; 37(4): 1499–501.
Wiedermann CJ. Anesth Analg 2010; 110(4): 1242.

Update on the Comparative Safety of Colloids: a systematic review of clinical studies – discussion

- Papers of Prof. Joachim Boldt (102 from 1999 onwards)
- 88 papers lacked approval of Ethics Committee → retraction
- Boldt strongly advocated the use of HES in place of albumin

- 2 in this review were positive for albumin
  - 5 others in this review compared different colloids
  - Prof. Joachim Boldt has been dismissed from his post as head of anesthesiology at the Klinikum Ludwigshafen in Germany, after an investigation uncovered multiple fraudulent activities relating to a clinical study published last year comparing the use of HES to 5% human albumin for cardiopulmonary bypass pump priming (HES better than albumin)
  - No Institutional Review Board approval
  - No written informed consent
  - No randomization process
  - No follow-up questionnaire

Cardiopulmonary bypass priming using a high dose of a balanced hydroxyethyl starch vs an albumin-based priming strategy. Boldt et al. Anesth Analg 2009; 109:1752-62

Groeneveld et al, Ann Surg 2011 Jan 6 [

Summary

EMA guidelines on adverse events (AE) rates:

- Common: > 1 AE per 100 administrations
- Uncommon: < 1 AE per 100 but > 1 AE per 1000 administrations
- Rare: < 1 AE per 1,000 but > 1 per 10,000 administrations
- Very rare: < 1 AE per 10,000 administrations

Haemovigilance schemes:

Data of Ireland and Greece

Hemolysis due to ABO incompatibility:	1	per 187,845 units
TACO:	1	per 10,436 units
Possible transfusion transmitted bacterial infection:	1	per 187,845 units
Anaphylaxis / hypersensitivity:	1	per 4,696 units
Incidence of SAEs:	0.9	per 10,000 whole blood units
	0.65	per 10,000 blood products
Incidence of non-SAEs:	12	per 10,000 whole blood units
	8.3	per 10,000 blood products

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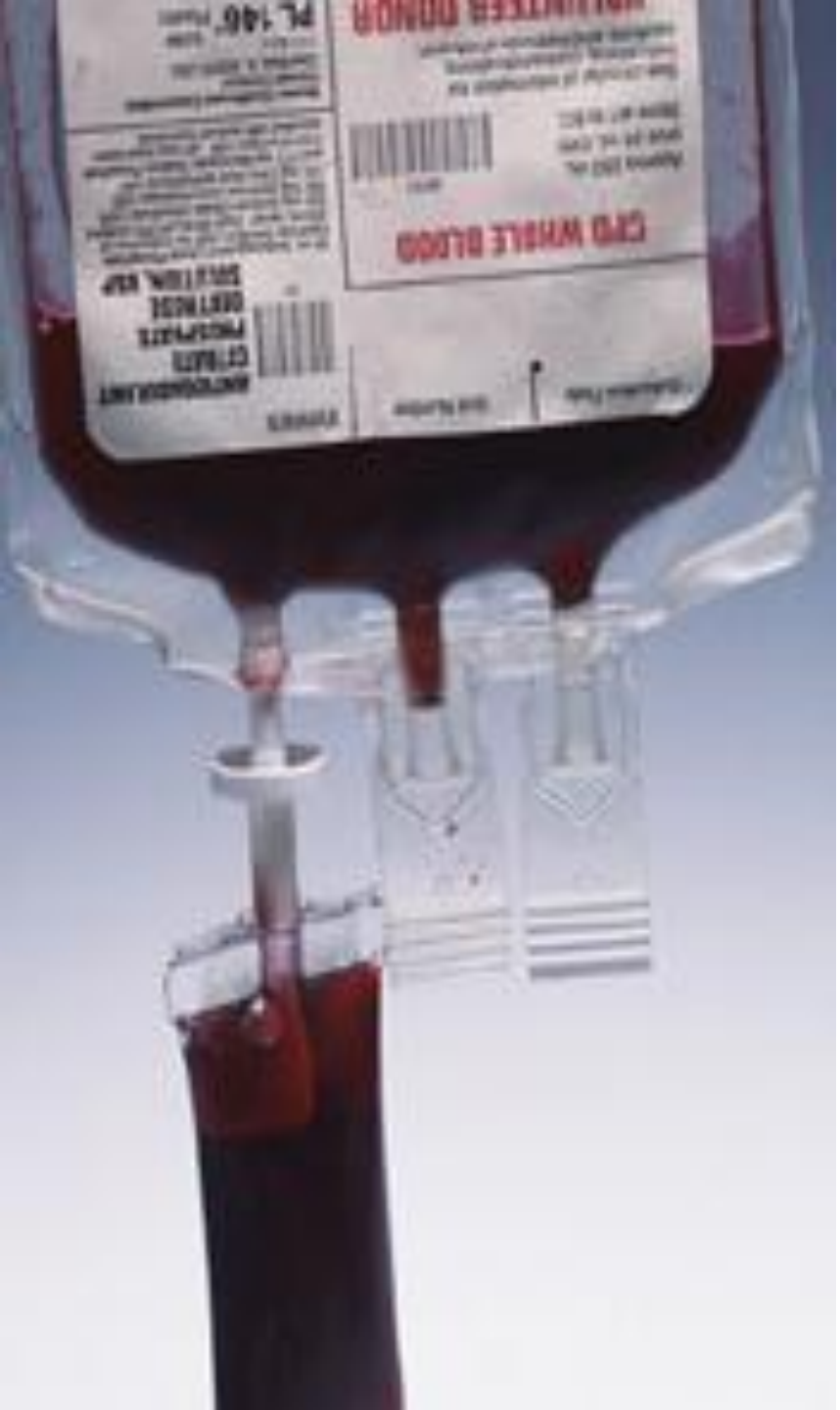
Summary

Medicinal alternatives to blood are:

- not that harmless
- even unsafe, at least some products, as considered by authorities,
- facing higher adverse events rate compared to blood components



Conclusion

- Whether alternatives to blood have a safety profile superior to blood should be reconsidered carefully

- Efforts should be made on data collection on (serious) adverse events rates of medical alternatives to blood

- Erythropoetin is administered unnecessarily and is more expensive than red cell transfusions.
Geelen-Gebroers et al. Blood Transfus 2010;8(1):s34.

- Blood transfusion committees should be informed on pro's and con's of blood alternatives

- Haemovigilance systems should consider whether alternatives to blood should be included in their objectives

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Questions?

p.strengers@sanquin.nl
www.sanquin.nl