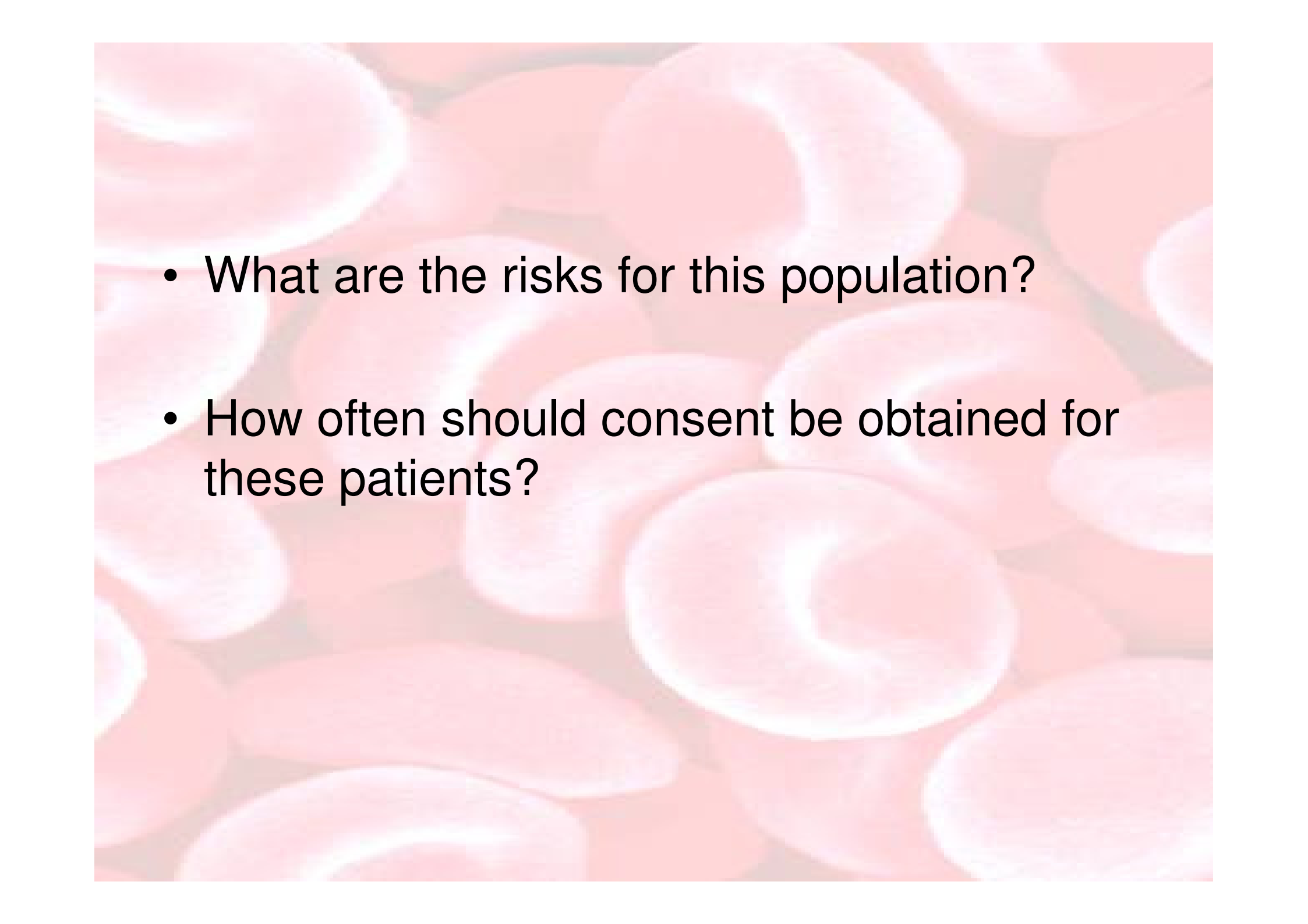


A microscopic view of numerous red blood cells, appearing as pinkish-red, biconcave discs, filling the entire background of the slide. The cells are slightly out of focus, creating a soft, textured effect.

INFORMED CONSENT

THE CHRONICALLY TRANSFUSED
PATIENT

Dr Bill Renwick RMH/Western Health

- 
- A background image showing a microscopic view of numerous red blood cells (erythrocytes) in a light pinkish-red hue. The cells are roughly circular and have a slightly bumpy or textured surface. They are scattered across the frame, with some in sharp focus and others blurred in the background.
- What are the risks for this population?
 - How often should consent be obtained for these patients?

Chronically Transfused – Who are they?

- Congenital Anaemias
 - Diamond-Blackfan, Aplastic Anaemia, Fanconi, Dyskeratosis Congenita,
 - Congenital Dyserythropoietic Anaemias
 - Congenital Haemolytic Anaemias
- Thalassaemia/Haemoglobinopathy
 - Beta thalassaemia, Sickle Cell Disease, HbH Disease,

Chronically Transfused – Who are they?

- Malignancy
 - Acute Leukaemia / Stem-cell Transplant
 - Dawson et al AML patients completing 1 Induction and 2 Consolidations – mean 35 units Haematologica 2007
 - Lymphomas / Myeloma
 - Solid malignancies – Breast, Bowel, Lung etc
 - Amount of transfusions very heterogenous
 - Time course may vary eg. cycles of chemotherapy, re-treatment after relapse

Chronically Transfused – Who are they?

- Myelodysplasia
 - Chronic long-term transfusions
 - Usually only intervention available
- Myeloproliferative
 - Idiopathic Myelofibrosis
 - Polycythaemia Rubra Vera - spent phase
- End-Stage Renal Disease

Chronically Transfused – Who are they?

- Non-Red cell Support
- Chronic Liver Disease – FFP, platelets
- Haemophilia - now recombinant products but an issue historically
- IVIG - multiple long-term users

Chronically transfused - How many are there?

- Shortt et al, described a prospective audit of 5132 red cell units in Victoria over 9 months - the “Bloodhound” audit Transfusion Epub July17 2009
- Of 4829 units transfused - Haem/Onc - 1623 (33.6%)
 - Haematinic deficiency - 137
 - Malignant Hamatology and SCT - 565
 - Non-Haem oncology - 470
 - Non-malignant Haem - 451

What are the risks of transfusion for this population?

- Risks are the same as for a single transfusion but multiplied +++
 - Infective - viral, bacterial etc
 - Physical - fluid overload, citrate toxicity in patients on red cell exchange programmes
 - Immune - transfusion reactions - acute, delayed; Febrile non-haemolytic, urticaria; TA- GVHD; TRALI; Post-transfusion purpura and Transfusion-related Immunomodulation (TRIM)

What are the risks of transfusion for this population?

- Specific to this population
- Alloimmunization (more risk and more of a problem)
 - Multiple exposures to foreign red cell Ags
 - Each antibody reduces the donor pool available
 - HLA antibodies - Stem-cell Transplant issues/ platelet refractoriness
- Iron overload
 - Beta thalassaemia, Sickle cell disease
 - Myelodysplasia
 - Stem-cell Transplantation

Beta Thalassaemia

- Chronic hypertransfusion mainstay of treatment
- Clinical course much improved - was previously limited to palliation or emergency
- In '60s - aim to maintain a “steady state” Hb 9 to 10 g/dL
- Improves oxygen-carrying capacity, cardiac status, growth, development and overall well being
- Intense effort to avoid isoimmunization
 - red cells are leukocyte-depleted, phenotype-matched
- Iron-overload - major issue

Iron overload in Thalassaemia

- Major cause of death in Thalassaemia major is cardiac disease from myocardial iron deposition
- Thalassaemic patients already have increased GI absorption of Fe, even when on transfusion programme
- Each unit red cells - 200 to 250 mg elemental Fe
- Iron can't be actively excreted, begin to sequester in other organs - heart, liver, endocrine organs

Iron overload in Thalassaemia

- Need iron chelation
- Clear improvement in OS
- Desferrioxamine (Desferral)
 - '70s s/c infusion
 - Major compliance problems
- Oral chelators
- Deferiprone (Ferriprox)
- Deferasirox (Exjade)
- Much better compliance



Iron Overload in Myelodysplasia

- Patients are regularly transfused.
- 2 Units red cells per month ~ 5 to 6 g Fe/year
- Iron overload after ~ 20 transfusions
- Data not as clear as for Thalassaemia
- Older patients with more co-morbidities - difficult to distinguish source of morbidities
- Most guidelines recommend considering iron chelation when serum ferritin > 1000 ng/mL Italian, Haematologica 2002; UK, Br J Haematol 2003, MDS Foundation (US) Am J Hematol 2008, NCCN (US), 2008

Iron Overload in Myelodysplasia

- However, some clinicians disagree and several articles published by the Mayo Clinic question the true impact of iron overload in MDS and myeloproliferative disorders:
- *Steensma, Myelodysplasia Paranoia: Iron as the new Radon, Leukemia Research 2008; Tefferi et al Am J Hematol 2009*
- No randomised prospective trials
- General opinion is to recommend chelation although in reality this is not being taken up by all clinicians or patients

Informed Consent

- Fundamental nature of informed consent has 3 basic elements:
 - 1. Benefits
 - 2. Risks
 - 3. Alternatives

Benefits

- In this population the benefits are clear:
 - Thalassaemia, SCD, Aplastic anaemia etc
Bone marrow insufficient supply
 - Malignant Haem/Onc - for chemotherapy to treat underlying disease - will need red-cell support
 - MDS/MF - majority will require red-cell support, clear evidence of benefits
 - End-stage renal disease - often require it despite EPO

Alternatives

- Thalassaemia, SCD, Aplastic anaemia
 - Manipulation of foetal Hb switching - Hydroxyurea, HDAC inhibitors
 - SCT/Immunosuppression - guidelines, availability for donor, risks
 - Gene Therapy
 - CHRONIC HYPERTRANSFUSION
- Malignancy - Haem/Onc
 - Iron, Folate, B12
 - Rare case reports of Jehovah's Witnesses treated without red-cell support Mazzi et al BMT 2003
 - MOST REQUIRE red cells in conjunction with their primary therapy
 - EPO - not approved in Australia, Controversy in US - ?worsened patients' outcomes

Alternatives

- MDS/Myeloproliferative
 - Recommended EPO in many guidelines depending on baseline level
 - EPO is not approved in Australia for this indication
 - Trials of interventions promising eg Azacitadine, Lenalidomide, JAK-2 inhibitors- but unproven expensive
 - SCT
- End-Stage Renal Disease
 - EPO approved and clearly beneficial

Informed Consent

- Options for these patients are severely limited
- Most are just adjuncts to the continued red cell transfusion support
- The decision for most patients is really about their underlying condition and whether they want treatment, rather than blood products
- Therefore the consent process for these patients should be as simple and as infrequent as possible

Informed Consent

- Options for Frequency of Consent
 - Every transfusion - clearly impractical in this population
 - Every Admission - Potentially appropriate for each course for induction/consolidation chemotherapy in AML/ALL but every MDS/Thal major outpatient transfusion is a separate admission
 - 6 monthly or yearly - is certainly the most appropriate for this population BUT
 - Need a system for registering this consent and when it expires