Great Ormond Street Hospital for Children

NHS Trust

Haematology & Transfusion in ITU

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Associated clinical guidelines/protocols:

- Blood Products in own folder (23/8/05) – Hospital Policies.
    1. Blood product ordering simple guide
    2. FFP and ordering
    3. Cryoprecipitate
    4. Granulocyte transfusions
    5. Crossmatching for surgical procedures
    6. Human albumin transfusions
    7. Platelet transfusions and ordering
    8. Red cell products
    9. Immunoglobulins
    10. Coagulation factors
- Neonatal Jaundice
- Sickle cell
- Thrombolysis (tPa) protocol

Fundamental Knowledge:

List of topics relevant to PIC that will have been covered in membership examinations.
They will not be repeated here.

Haemotology

- Normal haemopoiesis, haematological changes with age and sickness
- Haemoglobinopathies; diagnosis and principles of management
- Role of platelets, hypersplenism and thrombocytopenia, ITP
- Role of neutrophils, macrophages and lymphocytes
- Normal coagulation and coagulation disorders
- Blood groups and X-matching
- Potential infectious risks of transfusion
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Clinical syndromes

- Nutrient deficiency anaemia, haemolytic anaemias.

Information for Year 1 ITU Training (basic):

Year 1 ITU curriculum
Haematology:
- Haemolysis in critical care setting: causes, consequences, treatment
- DIC: causes, investigation, treatment
- Thrombocytopenia
- Thrombolysis, anticoagulation
- Coagulants in blood loss

Blood Products:
- Characteristics of stored blood/products
- Indications for irradiated blood products
- Indications for leucocyte transfusion.

Clinical Syndromes:
- Sickle cell crisis: (chest, neurological, priapism) diagnosis, exchange transfusion
- Acute sequestration in sickle cell disease

Please note:
The British Committee for Standards in Haematology (BCHS) publishes regular guidelines with which you must be familiar. Relevant guidelines are attached and can be downloaded from the website.
- **Transfusion guidelines in neonates in children, 2004**
- **Guidelines for the use of platelet transfusions 2003**
- **Guidelines for the use of fresh frozen plasma, cryoprecipitate and cryosupernatant 2004.**

http://www.bcshguidelines.com/

Haematology:

Haemolysis in critical care setting:
Haemolysis is the premature destruction of erythrocytes.
Multiple causes:
- **Red cell problems -** intrinsic membrane defects (sperocytosis), abnormal haemoglobins (HbS), erythrocyte enzyme defects (G-6-PD, PKD)
- **Immune mediated haemolysis:** (positive Coombs and DAT test)
  - **Auto-immune :** these can be broadly divided into warm & cold haemagglutinin disease, both of which can be idiopathic:
    Warm: e.g some drugs (penicillin, quinine etc) connective tissue disease (SLE, UC) lymphoproliferative disease (lymphoma) chronic inflammation, rhesus
    Cold: e.g Infections (mycoplasma, EBV, Parvovirus B19)
  - **Alloimmune:** Haemolytic disease of newborn and other transfusion reactions.
- **Non Immune mediated:**
  - **Trauma** e. g. extra-corporeal circulation e.g. CVVH, ECMO or artificial valves
  - **Microangiopathic:**, TTP, HUS, DIC, HELLP
  - Drugs
  - Infections - malaria

Haemolysis can be intra or extravascular (spleen)

Haemolysis is associated with a release of haemoglobin and lactic acid dehydrogenase (LDH). There is an increase in unconjugated bilirubin and urobilinogen and a decrease in haptoglobin.

http://www.emedicine.com/med/topic979.htm -general review haemolysis
Garratty et al- Drug-induced immune hemolytic anemia. Immunohematol.2004;20(3:138-46

Disseminated intravascular coagulation (DIC):
A definition of DIC and criteria for diagnosis are proposed by the DIC subcommittee of the International Society of Thrombosis and Haemostasis (ISTH):
> *Taylor FB et al Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost 2001; 86:1327 - 30.*

"An acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction"
It has the features of:
- Procoagulant activation
- Fibrinolytic activation
- Inhibitor consumption
- Biochemical evidence of end-organ damage or failure

It recognises overt and non- overt DIC and proposes the following scoring system:

1. Risk assessment: Does the patient have a underlying disorder known to be associated with overt DIC?
   If yes: proceed. If no: do not use this algorithm:

2. Order global coagulation tests (platelet count, prothrombin time (PT), fibrinogen, soluble fibrin monomers or fibrin degradation products)

3. Score global coagulation test results
   - platelet count *(>100 = 0; <100 = 1; <50= 2)*
   - elevated fibrin-related marker *(e.g. soluble fibrin monomers/fibrin degradation products)*
     (no increase: 0; moderate increase: 2; strong increase: 3)
   - prolonged prothrombin time
     (< 3 sec. = 0; > 3 sec. but < 6 sec. = 1; > 6 sec. = 2)
   - fibrinogen level
     (> 1.0 gram/l = 0; < 1.0 gram/l = 1)

4. Calculate score

5. If ≥ 5: compatible with overt DIC; repeat scoring daily
   If < 5: suggestive (not affirmative) for non-overt DIC; repeat next 1-2 days;

Taylor FB et al Thromb Haemost 2001; 86:1327-30

- A good review*: Levi M, Opal S. coagulation abnormalities in critically ill patients. Critical care 2006; 10: 222.*
- *http://www.sccm.org/specialties/pediatric/picu_course/Documents/catalog_pdf/19_dic.pdf* Peds CCM review powerpoint lecture on DIC

Thrombocytopenia
Occurs usually in the setting of sepsis/line infections, NEC or oncology patients admitted to ITU.
There are no absolute rules for threshold values to transfuse, although guidelines are suggested by the BCSH. It would seem sensible that if a patient is actively bleeding or at high risk of bleeding (ie sick neonate at risk of IVH) keep platelet count higher 50 -100 depending on the circumstances, otherwise 20 seems reasonable. We recommend >50 for invasive procedures – ordering & receiving platelets often takes time, SO liase early with transfusion.

Remember Heparin-Induced thrombocytopenia (HITS) which is not related to dose.

- *Napolitano LM Heparin induced Thrombocytopenia in the critical care setting: diagnosis and management. Crit Care Med 2006; 24:2898 – 2911*
BACKGROUND: Thrombocytopenia is a common occurrence in critical illness, reported in up to 41% of patients. Systematic evaluation of thrombocytopenia in critical care is essential to accurate identification and management of the cause. Although sepsis and hemodilution are more common etiologies of thrombocytopenia in critical illness, heparin-induced thrombocytopenia (HIT) is one potential etiology that warrants consideration.
OBJECTIVE: This review will summarize the pathogenesis and clinical consequences of HIT, describe the diagnostic process, and review currently available treatment options.
DATA SOURCE: MEDLINE/PubMed search of all relevant primary and review articles.
DATA SYNTHESIS AND CONCLUSIONS: HIT is a clinicopathologic syndrome characterized by thrombocytopenia (>/=50% from baseline) that typically occurs between days 5 and 14 after initiation of heparin. This temporal profile suggests a possible diagnosis of HIT, which can be supported (or refuted) with a strong positive (or negative) laboratory test for HIT antibodies. When considering the diagnosis of HIT, critical care professionals should monitor platelet counts in patients who are at risk for HIT and carefully evaluate for, a) temporal features of the thrombocytopenia in relation to heparin exposure; b) severity of thrombocytopenia; c) clinical evidence for thrombosis; and d) alternative etiologies of thrombocytopenia. Due to its prothrombotic nature, early recognition of HIT and prompt substitution of heparin with a direct thrombin inhibitor (e.g., argatroban or lepirudin) or the heparinoid danaparoid (where available) reduces the risk of thromboembolic events, some of which may be life-threatening
- *Newall F et al. HITS in children. J Paediatrics & Child Health. 39(4):289-292, May 2003.*
OBJECTIVE: To audit the frequency of heparinoid (standard heparin and low molecular weight heparin) use in a tertiary paediatric hospital, and to determine the occurrence of heparin-induced thrombocytopenia (HIT).
METHODS: A 1-week cross-sectional audit of all heparinoids given to inpatients at a tertiary paediatric hospital was undertaken and a retrospective medical record review of all suspected HIT cases at the tertiary paediatric centre over a 2-year period was carried out.
RESULTS: One hundred and sixteen patients received heparinoid medications over a 7-day period. An average of 29 children received heparin daily. The retrospective medical record review identified four patients with suspected HIT over a 2-year period. Two patients developed thrombotic complications, which were fatal in one patient.
CONCLUSION: Heparin is used frequently in paediatric tertiary hospitals, yet the occurrence of HIT in children is much lower than that reported in adults. Improved laboratory techniques could facilitate improved screening and diagnosis of this serious adverse drug reaction.
- *Roberts I Neonatal Thrombocytopenia: causes and management. Arch Dis Child Foetal ed 2003; 88: F. 359 -364.*

Thrombolysis & anticoagulation

- Peds CCM course lecture on pediatric thromboembolic disorders – very comprehensive
http://www.sccm.org/specialties/pediatric/picu_course/Documents/catalog_pdf/18_thromboembolic_disorders.pdf
- Our thrombolysis guidelines are based on the 7th ACCP Conference Guidelines *Monagle P et al Antithrombotic therapy in Children Chest 2004;126: 645S6^87*

The PICU protocol for thrombolysis requires consultant-level liaison for severe vascular occlusion including ICU, general surgical and haematology consultants (cardiology SPR if after cardiac catheter). Always look for predisposing characteristics in the child.

- The Thrombosis Interest Group of Canada has lots of antigoagulation guidelines, including pediatric ones here
  http://www.tigc.org/eguidelines/guidelines.htm

Blood Products:

Indications for Packed Cell Transfusion:
- The recently published **TRIPICU study** abstract is reproduced below. This is an important paper for our evidence base. Remember that the population studied consisted of stable children in intensive care.

Lacroix J et al. transfusion strategies for patients in paediatric intensive care units. In NEJM. 2007; 356:1609 -1619.

Background The optimal hemoglobin threshold for erythrocyte transfusions in critically ill children is unknown. We hypothesized that a restrictive transfusion strategy of using packed red cells that were leukocyte-reduced before storage would be as safe as a liberal transfusion strategy, as judged by the outcome of multiple-organ dysfunction.
Methods In this noninferiority trial, we enrolled 637 stable, critically ill children who had hemoglobin concentrations below 9.5 g per deciliter within 7 days after admission to an intensive care unit. We randomly assigned 320 patients to a hemoglobin threshold of 7 g per deciliter for red-cell transfusion (restrictive-strategy group) and 317 patients to a threshold of 9.5 g per deciliter (liberal-strategy group).
Results Hemoglobin concentrations were maintained at a mean (±SD) level that was 2.1±0.2 g per deciliter lower in the restrictive-strategy group than in the liberal-strategy group (lowest average levels, 8.7±0.4 and 10.8±0.5 g per deciliter, respectively; $P<0.001$). Patients in the restrictive-strategy group received 44% fewer transfusions; 174 patients (54%) in that group did not receive any transfusions, as compared with 7 patients (2%) in the liberal-strategy group ($P<0.001$). New or progressive multiple-organ dysfunction syndrome (the primary outcome) developed in 38 patients in the restrictive-strategy group, as compared with 39 in the liberal-strategy group (12% in both groups) (absolute risk reduction with the restrictive strategy, 0.4%; 95% confidence interval, –4.6 to 5.4). There were 14 deaths in each group within 28 days after randomization. No significant differences were found in other outcomes, including adverse events.
Conclusions In stable, critically ill children a hemoglobin threshold of 7 g per deciliter for red-cell transfusion can decrease transfusion requirements without increasing adverse outcomes.

- Neonates may be different and they may require higher thresholds than infants and children. The two main studies in this area heve conflicting results.

  ***Kirplanai H et al.** the premature infants in need of transfusion (PINT) study: a randomised controlled trial of restrictive (low) versus liberal (high). Transfusion threshold for extremely low birthweight infants. J Pediatr 2006:1 49:301-7.*

  OBJECTIVE: To determine whether extremely low birth weight infants (ELBW) transfused at lower hemoglobin thresholds versus higher thresholds have different rates of survival or morbidity at discharge.
  STUDY DESIGN: Infants weighing <1000 g birth weight were randomly assigned within 48 hours of birth to a transfusion algorithm of either low or high hemoglobin transfusion thresholds. The composite primary outcome was death before home discharge or survival with any of either severe retinopathy, bronchopulmonary dysplasia, or brain injury on cranial ultrasound. Morbidity outcomes were assessed, blinded to allocation.
  RESULTS: Four hundred fifty-one infants were randomly assigned to low (n = 223) or high (n = 228) hemoglobin thresholds. Groups were similar, with mean birth weight of 770 g and gestational age of 26 weeks. Fewer infants received one or more transfusions in the low threshold group (89% low versus 95% high, P = .037). Rates of the primary outcome were 74.0% in the low threshold group and 69.7% in the high (P = .25; risk difference, 2.7%; 95% CI -3.7% to 9.2%). There were no statistically significant differences between groups in any secondary outcome.
  CONCLUSIONS: In extremely low birth weight infants, maintaining a higher hemoglobin level results in more infants receiving transfusions but confers little evidence of benefit.

Bell EF. *Randomised trial of liberal versus restrictive guidelines for red blood cell transfusion in preterm infants. Pediatrics, 2005; 115; 1685 - 1691.9*
Free Access: *http://pediatrics.aappublications.org/cgi/content/full/115/6/1685*
OBJECTIVE: Although many centers have introduced more restrictive transfusion policies for preterm infants in recent years, the benefits and adverse consequences of allowing lower hematocrit levels have not been systematically evaluated. The objective of this study was to determine if restrictive guidelines for red blood cell (RBC) transfusions for preterm infants can reduce the number of transfusions without adverse consequences.
DESIGN, SETTING, AND PATIENTS: We enrolled 100 hospitalized preterm infants with birth weights of 500 to 1300 g into a randomized clinical trial comparing 2 levels of hematocrit threshold for RBC transfusion.
INTERVENTION: The infants were assigned randomly to either the liberal- or the restrictive-transfusion group. For each group, transfusions were given only when the hematocrit level fell below the assigned value. In each group, the transfusion threshold levels decreased with improving clinical status.
MAIN OUTCOME MEASURES: We recorded the number of transfusions, the number of donor exposures, and various clinical and physiologic outcomes. RESULTS: Infants in the liberal-transfusion group received more RBC transfusions (5.2 +/- 4.5 [mean +/- SD] vs 3.3 +/- 2.9 in the restrictive-transfusion group). However, the number of donors to whom the infants were exposed was not significantly different (2.8 +/- 2.5 vs 2.2 +/- 2.0). There was no difference between the groups in the percentage of infants who avoided transfusions altogether (12% in the liberal-transfusion group versus 10% in the restrictive-transfusion group). Infants in the restrictive-transfusion group were more likely to have intraparenchymal brain hemorrhage or periventricular leukomalacia, and they had more frequent episodes of apnea, including both mild and severe episodes.
CONCLUSIONS: Although both transfusion programs were well tolerated, our finding of more frequent major adverse neurologic events in the restrictive RBC-transfusion group suggests that the practice of restrictive transfusions may be harmful to preterm infants.
Andersen CC. Poor circulation, early brain injury, and the potential role of red cell transfusion in premature newborns. Pediatrics, 2006; 117; 1464 - 1466.

Characteristics of stored blood/products
The effects of storage on red cells and the impact on the critically ill as well reviewed in the following paper:
Ho J: Effects of storage on efficacy of red cell transfusion: when is not safe? Crit care Med 2003; 31:S687-S697.

Indications for irradiated blood products:
Please see BCSH guidelines – links above.
This is in order to avoid transfusion related GVHD. At risk groups include:-
- Congenital immunodeficiencies (eg Di George)
- Acquired immunodeficiency states
- Lymphoreticular malignancies
- Intensive chemo/radiotherapy
- Neonates having an exchange transfusion
- Neonates following antenatal transfusion

Clinical Syndromes:

Sickle Disease in ITU.
- Chest Crisis:
  Mak V, Davies S The pulmonary physician in critical care Illustrative case 6: Acute chest syndrome of sickle cell anaemia. Thorax. 58(8):726-728, August 2003.
  Free Access: http://thorax.bmj.com/cgi/content/full/58/8/726

  http://www.emedicine.com/ped/topic2096.htm - general review
- *Buchanan GR, Debaun MR, Quinn CT, Steinberg MH. Sickle cell disease. Hematology (Am Soc Hematol Educ Program). 2004;:35-47.*
  Free access: http://asheducationbook.hematologylibrary.org/cgi/content/full/2004/1/35
  This gives an indepth review of silent infarcts, outcome and predictors of outcome and novel therapies in sickle cell disease**.**

Information for Year 2 ITU Training (advanced):

> ### Year 2 ITU curriculum
> **Haematology:**
> - Severe anaemias: aplastic (including drug induced)
> - Role of colony stimulating factors in immune suppressed patients.
>
> **Blood Products:**
> - Use of activated factor concentrates
> - Indications for leucocyte transfusion.
>
> **Clinical Syndromes:**
> - Methaemaglobinaemia (PPHN module)
> - Carboxyhaemaglobinaemia (Burns module)
> - ARDS & MODS in patients requiring multiple transfusions.

Curriculum Notes for Year 2:

Haematology:

Aplastic anaemia:
Aplastic anemia is a syndrome of bone-marrow failure characterized by peripheral pancytopenia and marrow hypoplasia**.**
Acquired (drugs, radiation, infection – parvo virus, EBV) or inherited (Fanconis)

Drugs we use in ITU associated with risk of aplastic anaemia:-

Class of drug

Antibiotics	Chloramphenicol Sulfonamides Salazopyrine Co-trimoxazole
Anti-inflammatory	Indomethacin, Diclofenac
Anticonvulsant	Phenytoin Carbamazepine
Psychotropic	Phenothiazines

Treatment as per any reaction:
STOP drug, investigate, exclude other causes **AND** inform pharmacy
NB if strongly suspected/confirmed ALL serious drug reactions **notifiable** (yellow card)

Role of colony stimulating factors in immune suppressed patients
Always use with the advise of haematologists &/- oncologists.

- *Capo G et al. Management hematologic toxicities. J Support Oncol. 2004 Jan-Feb;2(1):65-79.*
- **Cochrane Review**. *Colony stimulating factors for chemotherapy induced febrile neutropenia 2000. Clark O et al.* Improved recovery time of neutrophils, but no impact on mortality.
- **Cochrane Reviews "**G-CSF and GM-CSF for treating or preventing neonatal infections"R Carr et al 2003 & Granulocyte transfusions for neonates with confirmed or suspected sepsis and neutropaenia" P Mohan. The available evidence suggts that these factors do not significantly improve outcome. When given as prophylaxis or adjuvant therapy during neonatal sepsis, and therefore cannot be recommended as a standard treatment in neonatal sepsis.

Blood Products:
Procoagulants in treatment of blood loss:
Firstly, investigate for and correct any abnormalities in haemostasis. This may involve the transfusion of platelets, FFPand or cryoprecipitate.
Medications can also be used as haemostatic agents.

- Aprotinin is a direct inhibitor of plasmin. In adults, it has been associated with increased rates of renal dysfunction or failure.
- Tranexamic acid is a lysine analogue that prevents binding of plasmin to fibrin, thereby preventing clots destruction.
- Desmopressin acts by releasing ultra-large von Willebrand factor multimers from endothelial cells thereby increasign plasma levels of von Willebrand factor and associated factor VIII. It is only efficacious in von Willebrand disease and haemophilia A
- recombinant activated factor VII -

Use of activated factor concentrates
Recombinant factor VIIa, has found new "off-label" uses in critical care, particularly in the fields of trauma and surgery.
Mathew P. The use of rVIIa in non-haemophilia bleeding conditions in paediatrics. Thromb Haemost 2004; 92:738-46.
It has been found to be benefit in adults with intracerebral haemorrhage in adults (Mayer SA NEJM 2005352:777-85), but has had no effect so far in preterm infants preventing IVH.
There have been a few successful cases of its use in neonates who have liver rupture at laparotomy for NEC (Filan M JPediatr 2005;147:857-9).
It has also been used for diffuse alveolar haemorrhage (Heslet L Crit Care 2006;10: R177)
Grounds RM Clinical experience and current evidence for therapeutic recombinant factor VII1 treatment in non-trauma settings. Crit Care 2005; 9:S29 - 36.

Indications for leucocyte transfusion.
Granulocyte transfusion are now a realistic option; healthy donors stimulated with G-CSF and/or dexamethasone yielding large numbers of granulocytes. Currently limited experience in children with severe neutropenic infection; controlled trials awaited to clarify clinical effectiveness and cost issues. Remember lung disease (ARDS) often worsens after transfusion.

Clinical Syndromes:

ARDS & MODS in patients requiring multiple transfusions.

- *See TRIPICU study referenced above.*
- *Hébert P et al. controversies in RBC transfusion in the critically ill. Chest 2007 131; 1583-1590. The summary from this paper:*

A summarization is as follows: (1) there is strong laboratory evidence suggesting that prolonged RBC storage may be deleterious; (2) observational studies report a number of associations between prolonged storage and adverse clinical outcomes, such as mortality and organ failure; however, (3) only two small adult trials have been published assessing clinical consequences of prolonged RBC storage. Given the importance of the question and limited evidence in humans, a definitive clinical trial is necessary to answer this question. If the age of transfused RBCs is in fact important, it would have major ramifications on the already limited blood supply. At this juncture, high-quality clinical evidence is not available.

- *Sanchez R, Toy P Transfusion-Related Acute Lung Injury Anesth Analg 2004;99:1623–4*
  Abstract:
  Transfusion-related acute lung injury (TRALI) is the leading cause of transfusion-associated mortality. TRALI occurs in children and adults, but the syndrome has not been reviewed from a pediatric perspective. We reviewed the literature on TRALI from a pediatric perspective. TRALI has been documented in pediatric patients, especially in the setting of hematologic malignancy. Additional TRALI cases have been reported in pediatric patients with a variety of diagnoses. TRALI is likely to be much more common than previously appreciated in the pediatric patient population. TRALI should be considered in the differential diagnosis of all pediatric patients who develop new acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) during or within six hours of a blood product transfusion. When a case of TRALI is suspected, a transfusion reaction report to the blood bank is important to initiate the investigation and identify the implicated donor. (c) 2005 Wiley-Liss, Inc.

Other sources of information:
Websites:
http://www.anaesthetist.com/icu/organs/blood/clinic.htm -Assessing Coagulation-AICU
References:
Zimmerman J. Use of blood products in sepsis: An evidence-based review. Crit Care Med 2004 Vol. 32, No. 11 (Suppl.)