



# Hematology 101 for the Pediatric Hospitalist

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2017 PEDIATRIC HOSPITAL MEDICINE

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## Disclosure

I have no relevant financial relationships to disclose

Dr. Courtney will discuss off-label uses of medications (we will discuss medications currently under clinical investigation)

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## Learning objectives

- Participants will be able to
  - (1) Understand the diagnosis, evaluation, and management of common and potential life-threatening conditions in patients with sickle cell disease
  - (2) Understand the diagnosis, evaluation, and management of bleeding and clotting disorders in pediatric patients
  - (3) Understand the selection of blood products. Understand the diagnosis, evaluation, and management of common transfusion reactions

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## Emergency Management of Sickle Cell Disease

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## Content outline

- Sickle cell disease 101
  - Epidemiology
  - Pathophysiology
  - Diagnosis
- Sickle cell emergencies and complication
  - Vaso-occlusive crisis/episode
  - Acute chest syndrome
  - Serious bacterial infection
  - Splenic sequestration
  - Aplastic crisis
  - Stroke
  - Priapism
- Providing clinical care for patients with sickle cell disease
  - Important history
  - Pneumococcal prophylaxis
  - Hydroxyurea
  - Transfusion
  - Exchange transfusion
- Latest trials (supplemental slides)

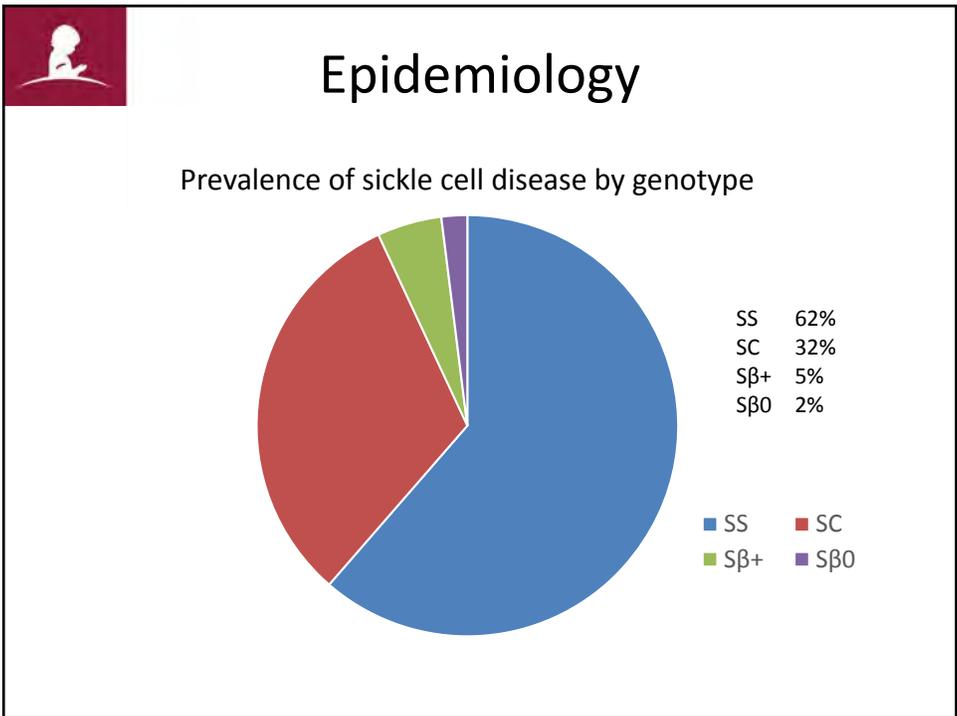


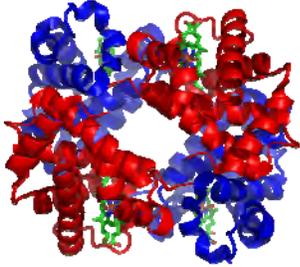
## Sickle cell disease 101



## Epidemiology

- Affects 100,000+ Americans
- S trait 1: 12
- SS 1 : 400





Richard Wheeler (Zephyris) 2007.  
<https://en.wikipedia.org/wiki/Hemoglobin>. Accessed 6/2017

## Pathophysiology

- Hemoglobin molecule  
2 alpha + 2 beta chains
- Qualitative beta chain defects  
Hb S = Glu → Val at position 6  
Hb C = Glu → Lys at position 6
- Quantitative beta chains defects (100+ mutations)  
 $\beta^{\circ}$  = no  $\beta$  globin production  
 $\beta^{+}$  = reduced  $\beta$  globin production



## Pathophysiology

- RBC deformation (sickling)  
Vasoconstriction  
Endothelial wall damage/ inflammation/ organ damage
- Hemolytic anemia
  - Constant destruction and inflammation cause both intravascular and extravascular hemolysis
  - Sickle RBC life span shortened by 1 – 3 weeks (from 90 – 120 days)
  - Baseline reticulocytosis (bone marrow compensation)



## Pathophysiology

Genotype	Disease	Baseline Hb	MCV	Clinical
$\beta^S\beta^S$ SS	Sickle Cell Anemia	6-9	-	Severe
$\beta^S\beta^C$ SC	Sickle Cell - HbC disease	9-12	-	Less frequent complications
$\beta^S\beta^+$ $S\beta^+$	Sickle - $\beta^+$ Thalassemia	10-13	↓	Milder
$\beta^S\beta^0$ $S\beta^0$	Sickle - $\beta^0$ Thalassemia	6-9	↓	Severe



## Diagnosis

- Newborn Screening (Hb electrophoresis)

Newborn Screen Result	Interpretation
FA	Normal
FAS	Sickle cell trait
FS	Sickle cell anemia (could be HbSS or HbS $\beta^0$ )
FSC	HbSC disease
FSA	Sickle (HbS $\beta^+$ )
FASBarts	Sickle cell trait with alpha thalassemia trait

- FAS (trait)  $\neq$  FSA (disease)



## Sickle cell emergencies and complications



### Vaso-occlusive Crisis/Episode

- Acute pain episodes caused by intravascular sickling and tissue infarction
- Triggers include change in temperature, exercise, and infections
- 50% of patients under age 10 and 60% of patients over age 10 have at least 1 crisis a year
- Early and aggressive management is key
- Management involves NSAIDs ± opioids and aggressive hydration



## VOC/VOE Management

- Pain assessment with appropriate pain scale
- Hydration : Fluid bolus. 1.5% maintenance (unless acute chest is suspected)
- NSAIDS : Ketolorac
  - Max 5 days
  - Limit/avoid in renal dysfunction or received within 30 days
- Opioid : Morphine or Hydromorphone
  - Hydromorphone preferred in renal insufficiency
  - Do not use Meperidine : increase risk of seizure
- Re-assess in 30 minutes, may need 2<sup>nd</sup> dose
- Consider hospitalization if in adequate pain control after 2 appropriate doses of opioids



## VOC/VOE Management

- Start PCA when appropriate
- Continuous pulse oximetry while on PCA ,  
Incentive spirometry
- Constipation prophylaxis while on opioid
- GI prophylaxis (Ranitidine) while on Ketolorac

\* See supplemental slides for more details



## Dactylitis

- Specific type of VOC/E in the hands and feet of infants and toddlers
- Tender, erythematous, and swollen hands and feet
- Occurs in 40% of children by age 2
- Treat like other VOC – fluids, pain management, etc.



<https://pedsinreview.aapublications.org/content/33/5/195#T1>



## Acute Chest Syndrome

- Definition – new infiltrate on chest x-ray plus one of following:
  - Fever
  - Tachypnea
  - Dyspnea
  - Hypoxia
  - Chest pain
- Given the definition, Sickle cell patients with reactive airway disease are highly at risk
- Incidence is highest in children ages 2-5



## Acute Chest Syndrome

- Cause is usually infectious – but not always

Cause	Episodes (N=670) (%)
Fat embolism, with or without infection	59 (8.8)
Chlamydia	48 (7.2)
Mycoplasma	44 (6.6)
Virus	43 (6.4)
Bacteria	30 (4.5)
Mixed infections	25 (3.7)
Legionella	4 (0.6)
Miscellaneous infections	3 (0.4)
Infarction	108 (16.1)
Unknown	306 (45.7)

*N Engl J Med 2000;342:1855-65.*



## Acute Chest Syndrome Management

- Fix lung inflammation and risk of white out from spreading inflammation
  - Antibiotics
  - Incentive spirometry
  - Oxygen as needed, bronchodilator
- Fix local sickling
  - Hydration (75% maintenance to prevent fluid overload)
  - Transfusion indicated in patients with hypoxia
  - Exchange transfusion in severe case, high baseline Hemoglobin , refractory to simple transfusion



## Serious bacterial infection

- Patients develop functional asplenia – high risk of infection with encapsulated organisms
- Infectious events can include
  - Sepsis (Pneumococcal)
    - 42% reduction of mortality rate in sickle cell patients age > 4 from 1999 to 2002 with introduction of pneumococcal vaccine in
  - Meningitis (*H. influenzae*)
  - Osteomyelitis (*Salmonella*)



## Fever Management

1. Immediate evaluation if temp > 38.5  
History, PE, CBC with diff, reticulocyte counts, blood culture, urine culture if suspect UTI
2. STAT antibiotics (Ceftriaxone or Fluoroquinolone)
3. Hospitalize if temp > 39.5 and ill-appearing
4. Immediate CXR for ACS symptoms
5. Consider osteomyelitis in patients with bone pain

<https://www.nhlbi.nih.gov/health-pro/guidelines/sickle-cell-disease-guidelines>  
Accessed 6/2017



## Fever Management

- All sickle cell patients with fever need immediate evaluation and Ceftriaxone
- Low risk patients may be managed outpatient with PO antibiotics  
(Many institutions do Amoxicillin for 48 hours)



## Splenic Sequestration

- One of leading causes of mortality in pediatric sickle cells
- Sickle event causes outflow obstruction → sudden, rapid enlargement of the spleen with trapping of a large volume of blood
- Occurs in children who have not yet had complete auto-infarction of the spleen
- S&S
  - Enlarged spleen
  - Drop in Hgb by  $>2$  g/dL (with brisk reticulocytosis and thrombocytopenia)
  - $\pm$  Hypotension, cardiac decompensation, hepatic involvement



## Splenic Sequestration

- Treatment
  - PRBC transfusion in emergent cases
  - \*\* Do not over transfuse as spleen will eventually release sequestered blood
  - Hydration
  - Serial examination
  - Consider splenectomy if patient has recurrent episodes (50% recurrence)



## Aplastic Crisis

- Transient marrow suppression by parvovirus
- Acute anemia, reticulocytopenia, no jaundice
- Spontaneous recovery in 7 – 10 days (may need transfusion)
- Pregnant health care workers
  - < 5 % chance of miscarriage (1<sup>st</sup> trimester), may consider avoiding if not immune

<https://www.cdc.gov/parvovirusb19/pregnancy.html> Accessed 6/2017



## Stroke

- Non-prophylaxis incidence
  - 7% (0.7% / year in the first two decades)
  - highest rate between age 5 – 10
- Mortality 9-29%
- Signs/Symptoms
  - Focal neurological deficit
  - Altered mental status
  - Seizure



## Stroke

- Management
  - Immediate diagnostic imaging
  - Consider exchange transfusion (goal HbS < 30%)
- Prevention
  - TCD
  - Chronic transfusion



## Priapism

- Prolonged, painful erection > 4hrs
- Caused by sickled RBC in corpora cavernosa
- Occurs as young as age 3
- 30% will have an episode by age 15
- Corpora cavernosa fibrosis and permanent erectile dysfunction if left untreated



## Priapism

- Management : consult Urology and Hematology in severe cases
  - Extra fluid
  - Pain control
  - Urination
  - Oral agents (Pseudoephedrine)
- Consider surgical intervention for cases > 4 hours
  - Penile aspiration, corporal irrigation, surgical shunting
- Exchange transfusion if fail aspiration



## Providing care for patients with sickle cell disease



## Important history

- Is prophylactic up to date ?
  - Penicillin
  - Vaccines
- Parvovirus status
- Acute chest/ Reactive airway disease history
- Stroke history
- Transfusion status
- Primary hematologist
- Education



## Penicillin Prophylaxis

- Oral penicillin until age 5 in all children
  - 125mg PO BID age <3
  - 250mg PO BID age 3+
  - \*Technically, guidelines say “consider withholding prophylaxis in HbSC and HbSβ\* (weak recommendation/low quality evidence)
- Continue past age 5 if
  - Splenectomy
  - History of invasive pneumococcal disease
  - Has not completed pneumococcal vaccines



## Hydroxyurea

- Increased HbF production, reduce inflammation, vasodilation
- Effective in infants and children with minimal side effects. Supported by large trials.
- Offered in children starting at age 9mo
- Do not hold during acute illness/hospitalization
- Hold if neutropenia, thrombocytopenia

\* See supplemental slides for more details

Wang, et al. *Lancet* 2011;377:1663-1672  
Kinney, et al. *Blood* 1999;94:1550-1554



## Transfusion

- Simple transfusion
  - DO NOT transfuse above Hb 10 – 11 g/dL due to risk of stroke
  - Risk of allosensitization in sickle cell patients
 Involve blood bank early
- Exchange transfusion
  - Acute life threatening situations
  - Rapidly reduce HbS to > 30% without increasing viscosity
  - Need line placement, warn blood bank

\* See supplemental slides for more details



## Case study

- 2 yo F HbSS with abdominal pain and “lying around” for 6 hours
- Exam : V/S T 37 HR 146/min RR 28/min BP 122/69 mmHg SpO2 100%  
In moderate distress (grimacing), still, hand on LUQ  
Spleen 3 cm from LCM
- What are the differential diagnosis?



## Case study

Differential diagnosis ?

- A) Vasooclusive crisis
- B) Constipation
- C) Splenic Sequestration
- D) Aplastic Crisis



### What is the differential diagnosis?

Vasooclusive crisis	0%
Constipation	0%
Splenic Sequestration	0%
Aplastic Crisis	0%

Source: <https://api.cvent.com/polling/v1/api/polls/sp-velpr1> Web Viewer Terms | Privacy & Cookies Edit



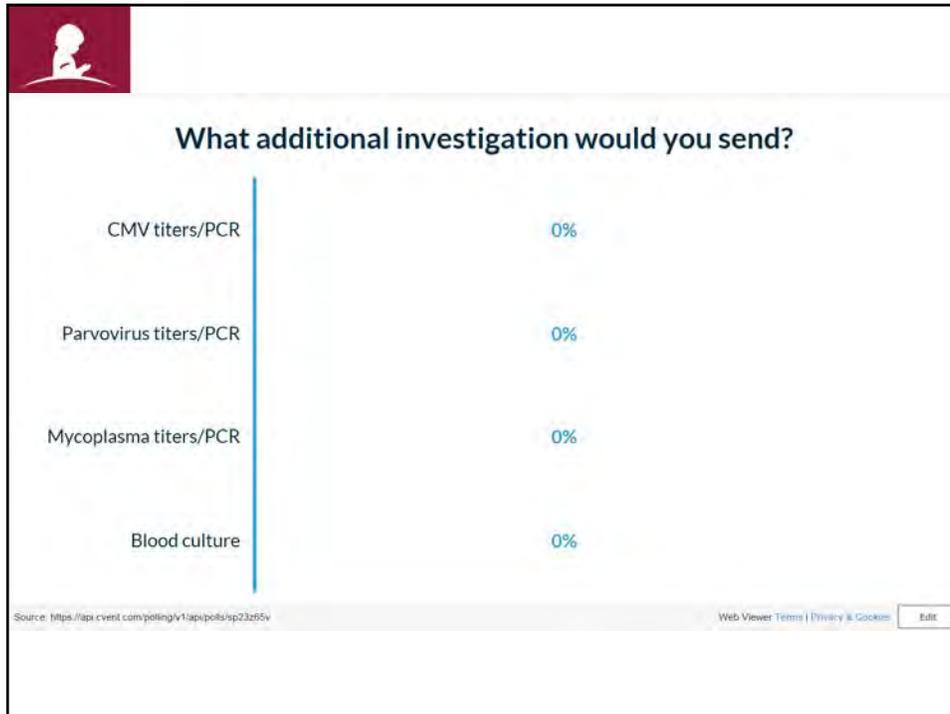
## Case study

- WBC 15.2 Hb 5.7 Hct 17.4 Plts 243K (N 60, B 3, L 28, Mo 8)  
MCV 91.3 fL  
Retic 0.18 % (  $0.0035 \times 10^6$  )
- Patient's baseline Hb was 8.5
- STAT PRBC transfusion (calculate to Hb of 8)  
Hydration at 1.5 maintenance  
Pain control : Scheduled Ketorolac and PRN Morphine  
Monitor Hb 1 hr after completion of transfusion, then Q6 hr  
Serial splenic examination
- What additional investigation would you send?



## Case study

- Additional investigation:
  - A) CMV titers/PCR
  - B) Parvovirus titers/PCR
  - C) Mycoplasma titers/PCR
  - D) Blood culture



## Case study

- Hospital course
  - The patient required 3 additional transfusions to keep Hb > 7
  - Pain slowly improved - Ketolorac stopped on day 4
  - Spleen size remained stable at around 2 cm below LCM, softer consistency each day
  - Discharged after 4 days
  - CBC before discharge
    - WBC 5.6 Hb 8.0 Hct 24.4 Plts 196K Retic 2.57% ( 0.0736 x 10<sup>6</sup>)
- Parvovirus studies positive
  - Parvovirus PCR Positive
  - Parvovirus IgM index 19.76
  - Parvovirus IgG index 2.04  
(specimens with index > 1.1 are considered positive)



## References

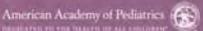
- Platt OS, Thorington BD, Brambilla DJ, et al. Pain in sickle cell disease. Rates and risk factors. *N Engl J Med* 1991;325:11-6.
- Gill FM, Sleeper LA, Weiner SJ, et al. Clinical events in the first decade in a cohort of infants with sickle cell disease. Cooperative Study of Sickle Cell Disease. *Blood* 1995;86:776-83.




## Clotting & Bleeding Disorders

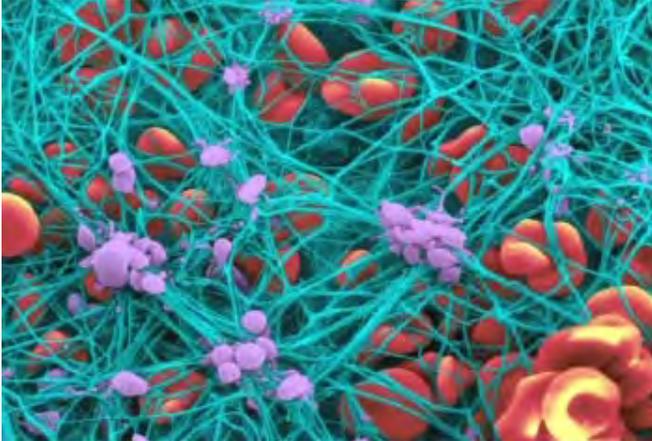
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## Clotting Disorders



Google Images.



## Question #1

- A 11yo F with a hx of a left tibial fracture just 1.5 weeks ago presents with swelling and pain of her left calf. An US revealed a DVT in her distal femoral, posterior tibial, and popliteal veins. What anticoagulant would you treat her with?
  - A.) Warfarin
  - B.) Low molecular weight heparin (LMWH)
  - C.) Heparin drip then transition to Coumadin in a few days
  - D.) Rivaroxiban
  - E.) Apixaban



**A 11yo F with a hx of a left tibial fracture just 1.5 weeks ago presents with swelling and pain of her left calf. An US revealed a DVT in her distal femoral, posterior tibial, and popliteal veins. What anticoagulant would you treat her with?**

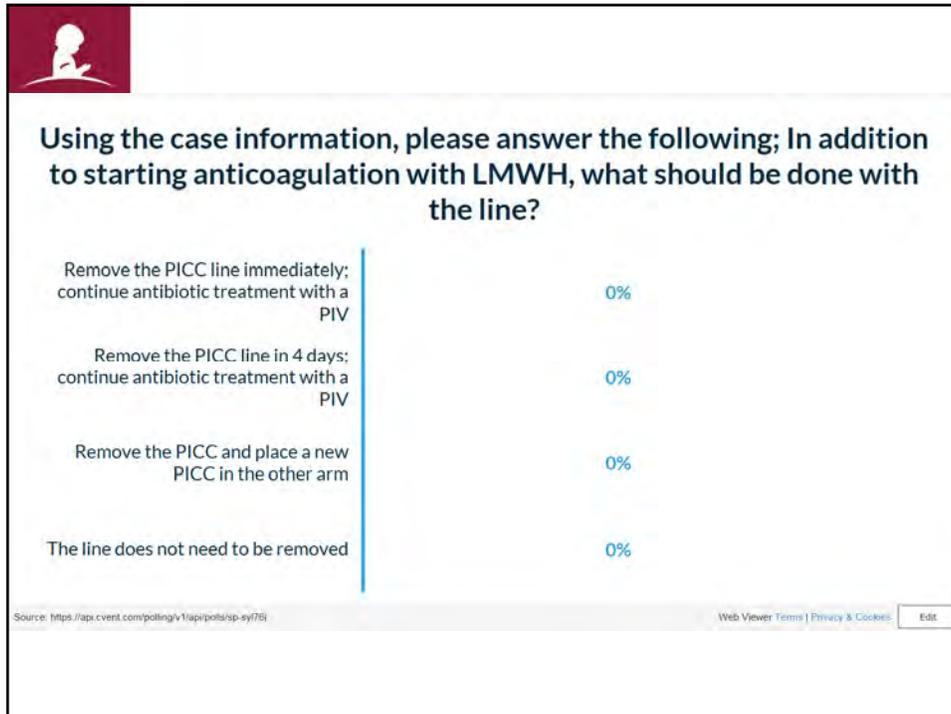
Warfarin	0%
Low molecular weight heparin (LMWH)	0%
Heparin drip then transition to Coumadin in a few days	0%
Rivaroxiban	0%
Apixaban	0%

Source: <https://api.cvent.com/polling/v1/api/pots/ep-61nyo> Web Viewer Terms | Privacy & Cookies Edit



## Question #2

- A 6yo F developed a necrotizing pneumonia and went home with IV antibiotics via a PICC line. Three days later she returns with a line associated DVT (Doppler ultrasound showed subclavian venous clot). She still has an additional week of antibiotics planned. In addition to starting anticoagulation with LMWH, what should be done with the line?
  - Remove the PICC line immediately; continue antibiotic treatment with a PIV
  - Remove the PICC line in 4 days; continue antibiotic treatment with a PIV
  - Remove the PICC and place a new PICC in the other arm
  - The line does not need to be removed



## Clotting Review

- Primary Hemostasis = formation of platelet plug
  - Platelet adherence → Activation → Aggregation
- Secondary Hemostasis = formation of the fibrin plug
  - Clotting factors in clotting cascade





## Clotting Disorders

- Pulmonary Embolism
  - Presentation – shortness of breath , chest pain, tachypnea, tachycardia, hypoxia, anxiety, hemoptysis
    - 2/3 are asymptomatic
    - DVT is absent more often than in adults
  - Diagnosis – Spiral CT/CT Angiogram (or VQ scan)
- Arterial thrombus
  - Presentation – diminished pulses and cool/mottled extremities
  - Diagnosis – US
  - #1 cause is an arterial catheter



## Clotting Disorders

- Cerebral Venous Sinus Thrombosis
  - Presentation– headache, blurred vision, cranial nerve palsy, papilledema, seizures
  - Diagnosis – CT (or MRI/V)
  - Causes – head/neck infections and trauma, Asparaginase
- Stroke
  - Presentation – Not always classic. May just be lethargy, hitting their head, behavioral changes, etc.
  - Diagnosis – MRI/A/V
    - Consider echocardiography to look for cardioembolic sources in cases of DVT → stroke or idiopathic stroke in young children
  - Causes – sickle cell disease, infection, cerebral arteriopathy, head/neck trauma, congenital cardiac disease, metabolic disease, etc.



## Clotting Disorders

- Post-thrombotic syndrome
  - Occurs in ¼ of children
  - Chronic complication of VTE with episodes of swelling, pain, visible collateral veins, and hyperpigmentation
  - Treatment - supportive - Compression stocking, limb elevation, avoidance of prolonged standing, and analgesics for pain
- You must do a thorough history and family history looking for thrombophilia and thrombosis risk factors before starting any patient on estrogen containing oral contraceptives



## Clotting Disorders - Workup Tips

- Wells criteria – not useful in children
- D-dimers – have some positive predictive value but not particularly useful
- CBC , PT/PTT/INR, and fibrinogen are needed prior to anticoagulation (to rule out other problems that would cause bleeding once anticoagulated) as well as a CMP (to evaluate for liver and renal function)



## Clotting Disorders - Workup Tips

- An inherited thrombophilia workup does not need to be done on every patient, may be done outpatient
- If there is a clear etiology for the clot (ie: a child with a malignancy and a CVL who develops a line-associated clot), a thrombophilia workup is not necessary.
- A workup should be considered for a child with an idiopathic clot or any child with a family or personal history concerning for an inherited thrombophilia

\* See supplemental slides for more details



## Clotting Disorders - Basics of Treatment

- Should be managed by pediatric hematologist when possible<sup>†</sup>
- Unfractionated heparin is preferred for cases that may need to return to the OR in short notice, may need reversed (protamine sulfate)
- Unfractionated heparin load boluses can be withheld in patients at high risk of bleeding
- Thrombolysis (systemic or local)/ thrombectomy for limb/life threatening clot<sup>†</sup>
  - Should be considered (based on institution comfort level) for large upper extremity/thoracic clots and high burden lower extremity clots.
- Otherwise, Lovenox is the treatment of choice in children
- Catheters should be removed after 3-5 days of therapeutic anticoagulation if possible

\* See supplemental slides for more details

<sup>†</sup>Monagle, P., et. al.



## Clotting Disorders - Basics of Treatment<sup>†</sup>

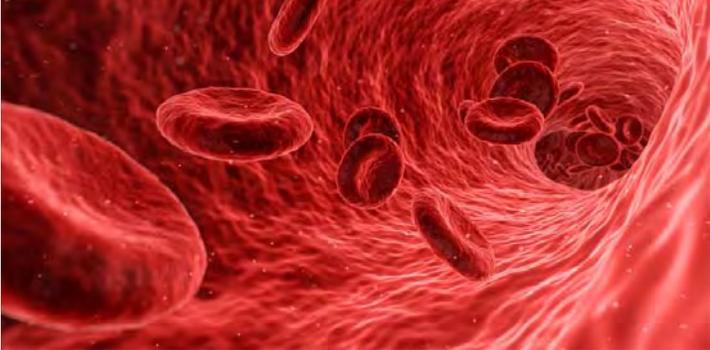
- Recommend prophylactic anticoagulation
  - Patients who had a line-associated clot but had to keep the line
  - Patients on chronic TPN
- These recommendations come from the CHEST guidelines.
- ASH will be releasing “Guidelines on the Treatment and Diagnosis of VTE” this year
- Few new Direct Oral Anticoagulants (DOACs) approved for adults and under clinical investigation for children

\* See supplemental slides for more details

†Monagle,P., et. al.



## Bleeding Disorders



Google Images.



## Question #3

- You are seeing a 4yo M with a hx of acute ITP. He presents with numerous petechiae and scattered bruises on his legs and other scattered involvement of his upper body. He denies epistaxis, gum bleeding, oral purpura, and other symptoms. CBC is normal except for a platelet count of  $8 \times 10^9/L$ . What treatment would you recommend?
  - A.) Observation only
  - B.) Oral prednisone
  - C.) IV Rituximab
  - D.) Platelet transfusion
  - E.) IVIG



### Using the case information, please answer the following; What treatment would you recommend?

Observation only	0%
Oral prednisone	0%
IV Rituximab	0%
Platelet transfusion	0%
IVIG	0%

Source: <https://api.cvent.com/polling/v1/api/polls/sp-bhho5l> Web Viewer Terms | Privacy & Cookies Edit



## Bleeding Differential

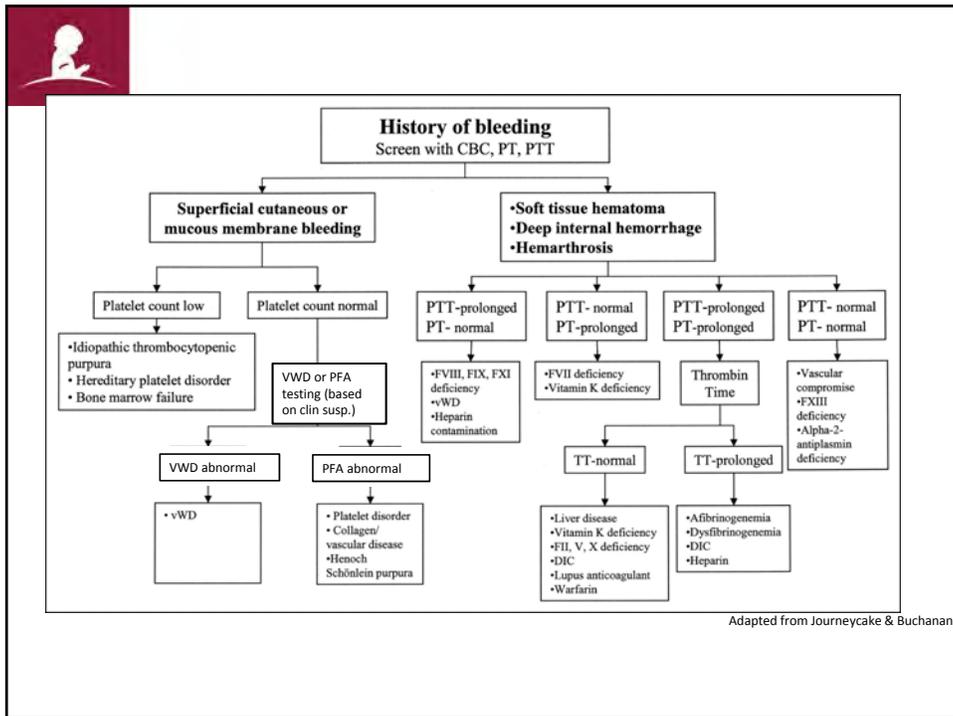
Inherited	Acquired
<u>Platelet Disorders</u> - <b>Von Willebrand Disease</b> - Rare function defects Hermansky-Pudlak, Chediak Higashi, MYH9-related disorders, Leukocyte Adhesion Deficiency III, etc. - Thrombocytopenia disorders Wiskott-Aldrich, TAR, DiGeorge syndrome, etc.	<u>Platelet disorders</u> - Autoimmune disorders – <b>ITP, NAIT</b> , etc - Drug induced quantitative & qualitative defects – <b>NSAIDS</b> , etc
<u>Coagulation Disorders</u> - <b>Hemophilia</b> , FXIII deficiency, Dysfibrinogenemia, Lupus Anticoagulant	<u>Coagulation Disorders</u> - Vitamin K deficiency - Acquired hemophilia A/B - Lupus Anticoagulant



## Workup of a Bleeding Child

- History is the most important part of the workup
  - Mucosal bleeding suggest platelet disorders
  - Deep bleeding suggests coagulation cascade disorders
  - Classic Red flags
    - Bleeding circumcision suggests Hemophilia
    - Menorrhagia suggests VWD
    - Sudden petechiae and mucosal bleeding on an otherwise healthy toddler suggest ITP
- Bleeding Score – questionnaire; scores  $\geq 2$  are abnormal

Score	-1	0	1	2	3	4
<b>Symptom</b>						
<b>Epistaxis</b>	-	No or trivial ( $\leq$ per year)	$>5$ per year OR $>10$ minutes duration	Consultation only	Packing, cauterization or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
<b>Cutaneous</b>	-	No or trivial ( $\leq 1$ cm)	$>1$ cm AND no trauma	Consultation only	-	-
<b>Minor wounds</b>	-	No or trivial ( $\leq$ per year)	$>5$ per year OR $>5$ minutes duration	Consultation only or Steri-strips	Surgical hemostasis or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
<b>Oral cavity</b>	-	No	Reported at least once	Consultation only	Surgical hemostasis or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
<b>Gastrointestinal tract</b>	-	No	Identified cause	Consultation or spontaneous	Surgical hemostasis, antifibrinolytics, blood transfusion, replacement therapy or desmopressin	-
<b>Tooth extraction</b>	No bleeding in at least 2 extractions	None done or no bleeding in 1 extraction	Reported, no consultation	Consultation only	Resuturing, repacking or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
<b>Surgery</b>	No bleeding in at least 2 surgeries	None done or no bleeding in 1	Reported, no consultation	Consultation only	Surgical hemostasis or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin
<b>Menorrhagia</b>	-	No	Reported or consultation only	Antifibrinolytics or contraceptive pill use	D&C or iron therapy	Blood transfusion, replacement therapy, desmopressin or hysterectomy
<b>Post-partum</b>	No bleeding in at least 2 deliveries	No deliveries or no bleeding in 1 delivery	Reported or consultation only	D&C, iron therapy or antifibrinolytics	Blood transfusion, replacement therapy or desmopressin	-
<b>Muscle hematoma</b>	-	Never	Post-trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring replacement therapy or desmopressin	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
<b>Hemarthrosis</b>	-	Never	Post-trauma, no therapy	Spontaneous, no therapy	Spontaneous or traumatic, requiring replacement therapy or desmopressin	Spontaneous or traumatic, requiring surgical intervention or blood transfusion
<b>Central nervous system</b>	-	Never	-	-	Subdural, any intervention	Intracerebral, any intervention
<b>Other *</b>	-	No	Reported	Consultation only	Surgical hemostasis, antifibrinolytics or iron therapy	Blood transfusion, replacement therapy or desmopressin





## Workup Tips

- Remember, NSAIDs and aspirin have anti-platelet effects and should be held for 5 days (NSAIDs), and 7-10 days (aspirin) prior to platelet function & VWD testing
- Atraumatic blood draws are important (prevents clumping on CBC, falsely elevated VIII levels, etc)



## Immune Thrombocytopenic Purpura (ITP)

- Usually preceded/triggered by a viral illness or vaccine (MMR)
- Caused by immune destruction of platelets
  - Autoantibodies (or allo/drug-dependent antibodies) against a platelet membrane antigen target platelets
- Mucocutaneous bleeding (petechiae/purpura, epistaxis, etc.) and 10% mild splenomegaly



## Immune Thrombocytopenic Purpura

- You should NOT see
  - Fever, bone pain, malaise, weight loss, neutropenia, lymphadenopathy → these should trigger an evaluation for malignancy
  - Deep bleeds (very rare with ITP)
- Diagnosis is clinical
  - Review of peripheral smear should be done prior to use of steroids
  - BM is not indicated



## Immune Thrombocytopenic Purpura

- Acute – Resolving within 3 month
  - 50% resolve in 2 months; 66% resolve by 3 month
- Persistent – lasting 3-12 months
- Chronic – lasting >12 months
  - 20-25% of patients have chronic cases. Age is the biggest risk factor (children > 10 are twice as likely to have chronic disease)
  - Spontaneous recovery still occurs in 1/3 of chronic cases



## Idiopathic Thrombocytopenic Purpura

- Treatment
  - There is growing evidence that treatment may not be necessary
    - 2011 ASH ITP Guidelines<sup>†</sup>: “The majority of patients with no bleeding or mild bleeding (defined...as skin manifestations only, such as petechiae and bruising) can be treated with observation alone regardless of platelet count (grade 1B).”
  - First line
    - IVIG
    - Steroids
    - Anti-D Immunoglobulin (Rhogam®, WinRho®)\*Rh+ children only
  - Second line/Chronic treatments
    - Rituximab
    - Splenectomy
    - Azathioprine, Cyclosporine, Tacrolimus, Interferon, etc.
- New Treatments
  - Thrombopoietin-stimulating agents (Eltrombopag or Romiplostim)

\* See supplemental slides for more details

<sup>†</sup>Neuhart, C., et. al.



## von Willebrand Disease

- Affects 1% of the population (Found in 5-20% of women with menorrhagia)<sup>†</sup>
- Caused by a quantitative or qualitative defect in von Willebrand Factor = defective platelet adhesion
- Mucocutaneous bleeding including epistaxis, bleeding after minor surgery (T&A or dental extraction), and menorrhagia
  - You rarely see deep bleeding (hemarthrosis, intramuscular hemorrhage, intracranial bleeding except with type 3)
  - A very thorough family history of bleeding should be taken

<sup>†</sup> Am J Hematol. 2005;79:220-8.



## von Willebrand Disease

- Subtypes:

Type	Problem	Inheritance
1	Mild/mod deficiency of vWF (Accounts for 70+%)	AD
3	Severe deficiency of vWF	AR
2A	Deficiency of high and intermediate weight vWF multimers	AD
2B	Abnormal vWF molecule with increase affinity for platelets → premature clearance of plt:vWF complex	AD
2M	Abnormal vWF molecule with decreased affinity for platelets	AD
2N	Abnormal vWF with reduced binding to VIII	AR



## von Willebrand Disease

- Initial workup for VWD
  - Can be ordered by a PCP with referral for abnormalities or clinical concern
  - VWF:Ag - Quantitative measure of VWF
  - VWF:RCo - Quantitative measure of VWF activity (Mix plasma with the antibiotic Ristocetin. Ristocetin induces a conformation change in VWF allowing the binding of VWF to GPIb receptor on platelets)
  - Factor VIII - Quantitative measure of Factor VIII
- Testing should be repeated if there is high suspicion as inflammation/stress/OCPs/etc can alter results
- Patients with type O blood have naturally lower levels of vWF antigen (~25% less than average)

\* See supplemental slides for more details



## von Willenbrand Disease

Type	Problem	VWF:Ag (IU/dL)	VWF:RCo (IU/dL)	FVIII (IU/dL)	VWF:Rco/VWF:Ag Ratio
1	Mild/mod deficiency of vWF (Accounts for 70+%)	<30	<30	Low or normal	>0.5-0.7
3	Severe deficiency of vWF	<3	<3	Extremely low (<10)	n/a
2A	Deficiency of high and intermediate weight vWF multimers	<30-200	<30	Low or normal	<0.5-0.7
2B	Abnormal vWF molecule with increase affinity for platelets → premature clearance of plt:vWF complex	<30-200	<30	Low or normal	Usually <0.5-0.7
2M	Abnormal vWF molecule with decreased affinity for platelets	<30-200	<30	Low or normal	<0.5-0.7
2N	Abnormal vWF with reduced binding to VIII	30-200	30-200	Very low	>0.5-0.7



## von Willenbrand Disease

- Treatment
  - DDAVP
    - Acts to stimulate the release of vWF from endothelial cells
    - Works for type 1 or very mild bleeding in other subtypes
    - 0.3mcg/kg IV (or 1 spray/150mcg intranasal in children <50kg and 2 sprays/300mcg in children ≥ 50kg)
    - Patients should have a DDAVP challenge to ensure they respond
    - Patients should be limited to maintenance hydration to prevent sodium abnormalities
    - Do not use in children <2 or patients with sodium regulation issues



## von Willenbrand Disease

- Concentrated vWF (ie: Humate®, Alphanate®, Koate®, etc)
  - Plasma derived vWF:VIII
  - Calculate dose:
    - Dose of concentrated VWF = U/dL desired rise in VWF \* Body weight (kg) \* 0.75
    - Minor surgery prophylaxis or mild bleeds = Target levels >30-50 IU/dL initially then as needed
    - Major surgery prophylaxis or severe bleeds = Target levels >100 IU/dL initially then maintain >50 IU/dL for 7-10 days
- Antifibrinolytics (Tranexamic Acid or Aminocaproic Acid; Lysteda® or Amicar®)
  - Useful for pre-surgery and pre-menses prophylaxis



## Hemophilia

- Occurs in 1 in 5000 males
- 80-85% of cases are Hemophilia A
- Inheritance is X-linked recessive
- Approximately 1/3 of all cases are caused by a new mutation (and 2/3 are inherited)
- Types
  - A – Factor VIII deficiency
  - B – Factor IX deficiency



## Hemophilia

- Classified by level of factor
  - Mild
    - >5 but <40% factor
  - Moderate
    - $\geq 1$  but  $\leq 5\%$  factor
  - Severe
    - <1% factor



## Hemophilia

- Presentation – Can see all forms of bleeding
  - Only 30% of children present with the classic bleeding circumcision
  - 1-2% of neonates have intracranial hemorrhage
  - Intramuscular hemorrhages
    - Vaccinations should be given subcutaneously whenever possible
  - Hemarthrosis
    - Often starts with an aura of tingling or warmth and is followed by pain, swelling, and decreased ROM
    - Recurrent bleeding into a joint (“target joint”) can lead to severe arthropathies
- Diagnosis – Prolonged PTT and decreased factor VIII or IX



# Hemophilia

- Treatment
  - Hemophilia A = Concentrated or Recombinant Factor VIII
    - Dose factor VIII (units) = U/dL desired rise \* body weight (kg) \* 0.5
  - Hemophilia B = Concentrated or Recombinant Factor IX
    - Dose factor IX (units) = U/dL desired rise \* body weight (kg)
  - In severe bleeds we want to achieve a level of 100% while levels of 30-40% may be sufficient for mild bleeding



# Hemophilia

- Treatment Tips
  - It is key to administer replacement factor immediately if a bleed is even slightly suspect - before any further workup is done (x-rays, CT scan, etc.)
  - Factor should be administered 5-10 minutes prior to surgery
  - Antifibrinolytic agents can be used as an adjunctive agent for mild mucocutaneous bleeding
  - FFP: 1 unit of FFP (200-250mL) only increases most factors by 2.5%



# Hemophilia

- Inhibitors
  - Antibodies against factor
  - Low titer inhibitors can be overcome by giving higher doses of concentrate
  - High titer inhibitors often can't be effectively overcome. Bleeds may need to be treated with rVIIa or activated prothrombin concentrate
- Prophylaxis
  - Standard of care all children once they begin to waddle
  - Goal to keep factor level >1% at all times
  - Often dosed 3\*/week for VIII and 2\*/week for IX



# Hemophilia

- New treatments
  - Long Acting Factor Concentrates†
    - Pegylation, fusion with Fc fragment of IgG, etc to increase half life of the factor
    - Two FDA approved in children for controlling bleeding, prophylaxis, and pre-op prophylaxis.
      - Efmoroctoctoglafa or Eloclate® = VIII = Prophylactic doses given q3-7 days.
      - Alprolix® = IX = prophylactic doses given q7-10 days.
    - Number of ongoing trials for additional drugs

†Wynn, T. T.



## Other Bleeding Disorders

- Platelet function disorders
  - Should be suspected when the platelet count is normal or only mildly decreased but the patient has mucocutaneous bleeding (and normal VWD testing).
  - A microthrombocytopenia may be noted
  - Dx – Platelet function assay
  - Platelet dysfunction can be seen in disorders such as Glanzmann Thrombasthensia, Bernard-Soulier, Wiskott-Aldrich, Chediak Higashi, etc.



## Other Bleeding Disorders

- Vitamin K deficiency bleeding in infants
  - In parental refusal for vitamin K
  - late bleeding 4.4 – 7.2 : 100,000 (81 times greater risk) <sup>†</sup>
- Acquired Vitamin K deficiency
  - Seen in children with malabsorption issues (CF, biliary atresia, etc) or severe malnutrition
- Liver failure
  - See normal VIII (vs. low in DIC)

<sup>†</sup> *MMWR Morb Mortal Wkly Rep.* 2013;62:901-2



## Other Bleeding Disorders

- DIC
  - Seen in severely ill children (sepsis, trauma, etc)
  - “Consumptive coagulopathy”= Extensive clotting → depletion of all clotting factors → bleeding
  - Treatment – fix underlying cause! Plus hematologic supportive care with platelets, FFP, cryoprecipitate, etc.



## Non-hematologic causes of bleeding/bruising

- Child abuse - a bleeding disorder does not rule out concomitant child abuse. Nor does abuse rule out a concomitant bleeding disorder.
- Vasculitis
- Infection – Neisseria meningitis, Rocky Mountain Spotted Fever, etc.
- Nutrition - Vitamin C Deficiency
- Connective Tissue Disorders – Ehlers Danlos, etc.



## Emergency Bleeding Treatment

- Platelet transfusion
- Steroids or IVIG – useful with autoimmune disease and drug-induced thrombocytopenia
- FFP
- Concentrate (vWF, Hemophilia, etc)
- PCC/FEIBA
- Recombinant Factor VIIa (NovoSeven®)
  - Life threatening bleeding with volume limitation, consult expert
  - Dosing 90mcg/kg q2Hr
- Emergent splenectomy (with autoimmune disorders)



## Resources

- American Society of Hematology (ASH) website contains “Pocket Guides” with high yield information as well as “Clinical Practice Guidelines” for a variety of hematological disorders
  - Pocket Guides: <http://www.hematology.org/Clinicians/Guidelines-Quality/Quick-Reference.aspx>
  - Clinical Practice Guidelines: <http://www.hematology.org/Clinicians/Guidelines-Quality/Guidelines.aspx>



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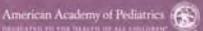



## Recognition and Management of Transfusion Reactions

Jitsuda Sitthi-amorn, MD  
Staff Physician/Hospitalist Program  
St. Jude Children's Research Hospital











## Case 1

- A 2 year old girl with sickle cell disease is getting PRBC transfusion for aplastic crisis. The patient was afebrile prior to the transfusion. You were notified that the patient is now having 39°C fever. Other vital signs are stable except for mild tachycardia.
- What is the next step of management?
  - A. Stop transfusion and obtain transfusion reaction work up
  - B. Obtain blood culture and start board spectrum antibiotics
  - C. Obtain chest X-ray
  - D. No need to do anything as the other vital signs are stable.



## Case 2

- A 13 year boy (45 kg) recently diagnosed with acute myeloid leukemia is receiving platelet transfusion with single donor apheresis platelets for platelet counts of  $8 \times 10^3$  microL. He also received 1 unit of PRBC earlier and is undergoing twice maintenance hydration for tumor lysis syndrome. You were asked to evaluate the patient for sudden onset tachypnea.
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  - D. No need to do anything as this is likely transfusion associated circulatory overload



## Content outline

- Blood product selection and administration
- Infection
- Acute hemolytic transfusion reaction
- Delayed hemolytic transfusion reaction
- Urticarial reaction
- Anaphylaxis
- Febrile non hemolytic transfusion reaction
- TRALI
- TACO
- TA-GVHD



## Content outline

- **Blood product selection and administration**
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- TRALI
- TACO
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## Products: Red cells

- Leukoreduction
  - $< 5 \times 10^6$  WBC per unit
  - Reduce febrile non-hemolytic transfusion reaction, CMV , HLA-alloimmunization
  - Considered CMV-safe
- Irradiation
  - Inactivates T-lymphocyte
  - Prevents TA-GVHD
  - Immunocompromised patients , family donors
- Washed
  - Plasma removal
  - Patients with severe allergic reaction, severe Ig-A deficiency
- CMV negative
  - From CMV negative donors
  - CMV negative patients

\* controversial, defer to institutional guideline



## Products: Red cells

- Dose : 10 – 15 mL/kg
- Infuse over 3 – 4 hours  
(not longer than 4 hours, slowly over first 15 min)
- Expected Hb increase 2-3 g/dL for each 10 mL/kg
- PRBC volume (ml) =  $3.5 \times \Delta\text{Hb} \times \text{weight (kg)}$
- Consider slower transfusion in patients with chronic severe anemia and circulatory overload



## Products : Platelets

- Whole blood derived platelets
  - Prepared from multiple units of whole blood
- Apheresis platelets
  - Collected from a single donor by apheresis
  - Lower risk of transfusion transmitted infection and contamination
- Dose Infant : 10 mL/kg
  - Whole blood derived platelets : 1 unit/ 10kg
  - Apheresis platelets : 1 unit (wt > 30kg) , ½ unit (wt 10-30 kg)
- Infuse over 30 – 60 minutes
- Expected increase : 50K – 100K/mm<sup>3</sup> for each 10 mL/kg



## Products: Plasma

- Fresh frozen plasma
  - Coagulation factors
  - FP-24 (frozen 8 – 24 hr after collection) has slightly reduced factor V, VIII
  - 10 – 20 mL / kg over 30 – 60 minutes (approximately 25% increase)
- Cryoprecipitate
  - Factor VIII, factor XIII, Fibrinogen, von Willibrand factor
  - Bleeding secondary to fibrinogen abnormality
  - 1 – 2 unites / 10 kg (max 10 units) over 30 – 60 minutes (approximately 100 mg/dL increase)

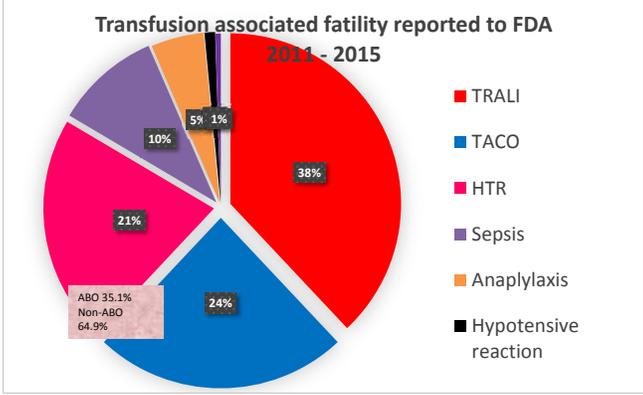


## Content outline

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### Transfusion associated fatality reported to FDA 2011 - 2015



Category	Percentage
TRALI	38%
TACO	24%
HTR	21%
Sepsis	10%
Anaphylaxis	5%
Hypotensive reaction	1%
ABO	35.1%
Non-ABO	64.9%

■ TRALI  
■ TACO  
■ HTR  
■ Sepsis  
■ Anaphylaxis  
■ Hypotensive reaction

FDA/CBER. Fatalities reported to FDA following blood collection and transfusion. Annual summary for fiscal year 2015. Accessed 5/2017



## Infection : Viral

- Transfusion transmitted infection, estimated US data
  - Hepatitis B 1: 1,208,000
  - Hepatitis C 1: 1,149,000
  - HIV 1: 1,467,000
  - West Nile, parasitic disease – uncommon
- Lower incidence in first time donors compared to general population
- Directed donors had similar rate of positive infection compared to volunteers

Transfus Med Rev. 2012;26:119-28.  
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 JAMA. 2000;201:229-35.  
 Transfusion. 2013;53:1250-6  
 Weinstein R, <http://www.hematology.org/Clinicians/Guidelines-Quality/Quick-Reference.aspx> Accessed 6/2017



## Infection : Bacterial

- Blood product contamination
  - Platelets 1: 2000 units
  - PRBC 1: 30,000 units
- Transfusion transmitted infection
  - Platelets 10 : 1,000,000 units
  - PRBC 0.2 :1,000,000 units
- Organisms
  - Platelets – gram positive
  - PRBC – gram negative (cryophilic)
  - Yersinia enterocolitica* , *Pseudomonas fluorescens*

Transfusion. 2001;41:1493-9  
 Semin Hematol. 2001;38:20-6



## Infection : Bacterial

- Presentation
  - Fever (> 39C , > 2C from starting transfusion)
  - Chills
  - Hypo/hypertension, tachycardia, tachypnea
- Management
  - Stop transfusion
  - Transfusion reaction evaluation
  - Antibiotics : broad spectrum coverage (including CONS, pseudomonas)  
Vancomycin + broad spectrum beta-lactam/aminoglycoside

Transfusion. 2001;41:1493-9



## Acute hemolytic transfusion reaction (AHTR)

- Hemolysis within the first 24 hours
- Etiology
  - ABO incompatibility
  - Minor RBC antigens (less common)
  - Plasma products (rare)
- Mostly due to clerical error
- Most common cause of transfusion related death in US 1976 - 1985
- Estimated fatal AHTR (US) : 1 : 1,972,000

Transfus Med Hemother. 2008;35:346-53  
JAMA. 2016;316:2025-35



## Acute hemolytic transfusion reaction (AHTR)

- Presentation
  - Fever, chills, back pain, oozing from IV sites, hypotension, acute renal failure
  - Hemoglobinemia, hemoglobinuria, DAT+, evidence of DIC
- Management
  - Stop transfusion
  - Stabilize
  - Transfusion reaction work up
  - hydration\*\* (UOP at least 1 mL/kg/hr for at least 18 -24 hr)
  - Treat DIC, pressor PRN
  - Monitor : DIC, renal failure, chemistry, serial Hemoglobin

Transfus Med Hemother. 2008;35:346-53



## Delayed hemolytic transfusion reaction (DHTR)

- Hemolysis 1 -2 weeks after transfusion (3 – 30 days)
- Amnestic response to previously exposed RBC antigen (previous transfusion, pregnancy, shared needles, transplant)
- Presentation
  - Anemia
  - Fever and jaundice
  - New RBC alloantibody
- Management
  - Monitor until hemolysis is over



## Anaphylaxis

- 1 in 20,000
- Ig-E mediated, cause by antibody to donor plasma protein
- Described in IgA deficiency, donor ingestion of allergen
- Presentation : sudden onset of
  - Hypotension
  - Angioedema
  - Wheezing
- Management
  - Stop transfusion
  - Treat anaphylaxis (Epinephrine, fluid, antihistamines, steroid)
- Prevention : Plasma removal, washing
- Urticarial rash alone is common and benign



## Allergic (urticarial) reaction

- 1-3%
- Caused by antibody to donor plasma proteins
- Presentation
  - urticarial rash, itching, flushing
  - mild wheezing
- Management
  - Stop transfusion, transfusion reaction work up
  - May resume if resolved



## Febrile non hemolytic transfusion reaction

- Temperature increase greater than 1°C, not due to other cause
- Cytokines occurred during storage
- Estimated incidence 0.1 – 1 per 100
- Benign, but must exclude AHTR, sepsis, and TRALI
- Management
  - Stop transfusion and transfusion work up
  - Decision to proceed depends on patient’s clinical status
- Prevention
  - Leukoreduction
  - No evidence to support pre-medication

Transfusion. 2008;48:2285-91



## Transfusion associated acute lung injury (TRALI)

- New episode of acute lung injury within 6 – 24 hr without other cause
- 1 in 10,000  
Highest cause of death from transfusion (10 – 20% fatal)
- Mostly reported with plasma products  
Pulmonary endothelial injury causing by “primed” recipient neutrophils and donor anti-HLA antibodies
- Since Nov 2006, no FFP/apheresis platelets from female with history of pregnancy (unless anti-HLA antibody negative)

Expert Rev Hematol. 2016;9:497-508



## Transfusion associated acute lung injury (TRALI)

- Presentation
  - Hypoxemia
  - Bilateral pulmonary infiltration (without circulatory overload)
  - Fever, hypotension, frothy sputum
  - Usually improved within 96 hours
- D/Dx : TACO, other cause of ARDS, ATHR, Sepsis, Anaphylaxis
- Management : Supportive care, Defer implicated donor
  - Most patients require mechanical ventilation
  - Steroid is controversial



## Transfusion associated circulatory overload (TACO)

- 1% of transfusion
- Clinical presentation
  - Respiratory distress, hypertension, pulmonary edema during or right after transfusion
  - Response well to diuretics
- Differential diagnosis : TRALI, anaphylaxis, other cause of cardiac failure / PE
- Management
  - Diuretics
  - Respiratory support
- Prevention
  - Avoid transfusing too much or too fast



## Transfusion associated Graft Versus Host Disease (TA-GVHD)

- Engraftment of donor lymphocyte  
Immunocompromised patients, partial HLA match
- Clinical presentation
  - 4 – 30 days
  - Erythematous MP rash that progress to erythroderma or TEN
  - Anorexia, profound diarrhea
  - Acute hepatic injury
  - Pancytopenia
  - 80 – 90% mortality rate
- Prevention
  - Irradiation



## Case 1

- A 2 year old girl with sickle cell disease is getting PRBC transfusion for aplastic crisis. The patient was afebrile prior to the transfusion. You were notified that the patient is now having 39°C fever. Other vital signs are stable except for mild tachycardia.
- What is the next step of management?
  - A. Stop transfusion and obtain transfusion reaction work up
  - B. Obtain blood culture and start broad spectrum antibiotics
  - C. Obtain chest X-ray
  - D. No need to do anything as the other vital signs are stable.



**A 2 year old girl with sickle cell disease is getting PRBC transfusion for aplastic crisis. The patient was afebrile prior to the transfusion. You were notified that the patient is now having 39C fever. Other vital signs are stable except for mild tachycardia. What is the next step of management?**

Stop transfusion and obtain transfusion reaction work up	0%
Obtain blood culture and start broad spectrum antibiotics	0%
Obtain chest X-ray	0%
No need to do anything as the other vital signs are stable.	0%

Source: <https://api.cvent.com/polling/v1/api/polls/spt22ctb9> Web Viewer Terms | Privacy & Cookies Edit



## Fever during transfusion

Stop transfusion  
 Stabilize patient  
 Transfusion reaction work up

Cause of fever	Supportive findings	Management
AHTR	Chills, back pain, hypotension hemoglobinemia, hemoglobinuria + DAT DIC	Hydration Maintain adequate urine output
TRALI	Hypotension Diffuse bilateral infiltration Transient leukopenia May not response to diuretics	Respiratory support Steroid is controversial
Sepsis/ Bacterial infection	Chills Leukocytosis DIC Positive blood culture	Antibiotics
FNHTR	No other symptoms	None



## Case 2

- A 13 year boy (45 kg) recently diagnosed with acute myeloid leukemia is receiving platelet transfusion with single donor apheresis platelets for platelet counts of  $8 \times 10^3$  microL. He also received 1 unit of PRBC earlier and is undergoing twice maintenance hydration for tumor lysis syndrome. You were asked to evaluate the patient for sudden onset tachypnea.
- What is the next step of management?
  - A. Stop transfusion and obtain transfusion reaction work up
  - B. Obtain blood culture and start board spectrum antibiotics
  - C. Obtain chest X-ray
  - D. No need to do anything as this is likely transfusion associated circulatory overload



**Using the case information, please answer the following; What is the next step of management?**

Stop transfusion and obtain transfusion reaction work up	0%
Obtain blood culture and start board spectrum antibiotics	0%
Obtain chest X-ray	0%
No need to do anything as this is likely transfusion associated circulatory overload	0%

Source: <https://api.cvent.com/polling/v1/api/poll/isp-nczj9> Web Viewer Terms | Privacy & Cookies Edit



## Respiratory distress during transfusion

Stop transfusion  
 Stabilize patient  
 Transfusion reaction work up

Cause of respiratory distress	Supportive findings	Management
TRALI	Fever Hypotension Diffuse bilateral infiltration Transient leukopenia May not response to diuretics	Respiratory support Steroid is controversial
TACO	Usually do not have fever Hypertension Diffuse bilateral infiltration No change in WBC count Response to diuretics	Diuretics Cardiorespiratory support
Anaphylaxis	Urticaria Bronchospasm Angioedema Hypotension	Treat anaphylaxis



## Take home points

- Stop transfusion and send transfusion reaction work up whenever there is a suspicion of transfusion reaction



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<http://www.hematology.org/Clinicians/Guidelines-Quality/Quick-Reference.aspx> Accessed 6/2017



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## Questions

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