



**Race for INR Reduction:  
Review of prothrombin  
complex concentrate  
(PCC) use in a  
pediatric hospital**



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**Disclosures**

- Off-label use will be discussed
- Due to multiple prothrombin complex concentrates studied, brand names will be utilized to differentiate and eliminate confusion.

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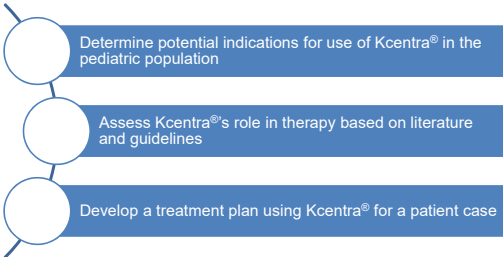
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**Objectives**



- Determine potential indications for use of Kcentra® in the pediatric population
- Assess Kcentra®'s role in therapy based on literature and guidelines
- Develop a treatment plan using Kcentra® for a patient case

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### Abbreviations

<b>AMS</b>	Altered mental status	<b>ICU</b>	Intensive care unit
<b>ATC</b>	Acute trauma of coagulopathy	<b>INR</b>	International normalized ratio
<b>CRRT</b>	Continuous renal replacement therapy	<b>IV</b>	Intravenous
<b>CT</b>	Computed tomography	<b>MVC</b>	Motor vehicle collision
<b>DIC</b>	Disseminated intravascular coagulation	<b>OR</b>	Operating room
<b>DVT</b>	Deep vein thrombosis	<b>PCC</b>	Prothrombin complex concentrate
<b>ED</b>	Emergency department	<b>PE</b>	Pulmonary embolism
<b>EVD</b>	Extra ventricular drain	<b>PK/PD</b>	Pharmacokinetics/dynamics
<b>FDA</b>	Food and drug administration	<b>PRBC</b>	Packed red blood cells
<b>FFP</b>	Fresh frozen plasma	<b>PT</b>	Prothrombin time
<b>GCS</b>	Glasgow coma scale	<b>SDH</b>	Subdural hemorrhage
<b>GI</b>	Gastrointestinal	<b>TBI</b>	Traumatic brain injury
<b>HPI</b>	History of present illness	<b>TXA</b>	Tranexamic acid
<b>ICH</b>	Intracranial hemorrhage	<b>VKA</b>	Vitamin K antagonist



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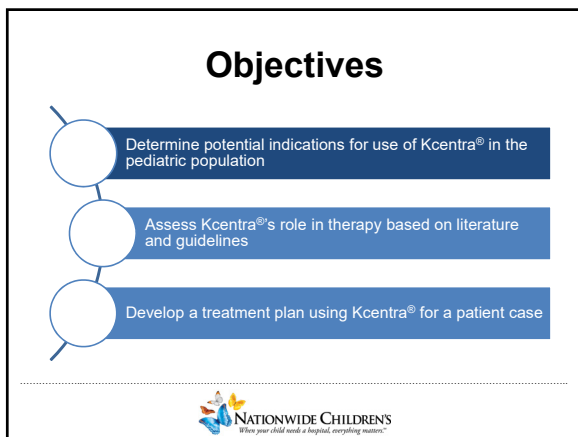
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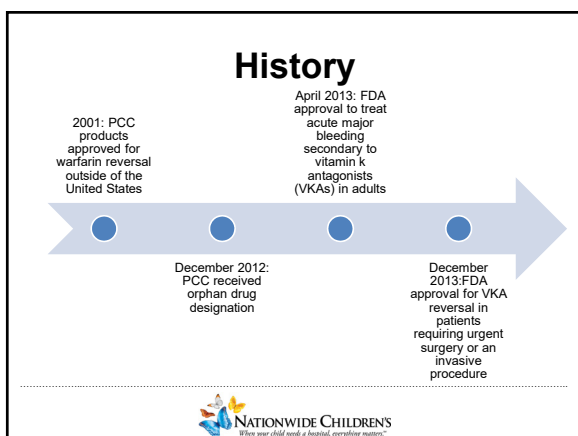
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## Components

Table 7: Composition per Vial of Kcentra<sup>®</sup>

Ingredient	Potency Range for 500 units	Potency Range for 1000 units
Total protein	120–280 mg	240–560 mg
Factor II	380–800 units	760–1600 units
Factor VII	200–500 units	400–1000 units
Factor IX	400–620 units	800–1240 units
Factor X	500–1020 units	1000–2040 units
Protein C	420–820 units	840–1640 units
Protein S	240–680 units	480–1360 units
Heparin	8–40 units	16–80 units
Antithrombin III	4–30 units	8–60 units
Human albumin	40–80 mg	80–160 mg
Sodium chloride	60–120 mg	120–240 mg
Sodium citrate	40–80 mg	80–160 mg
HCl	Small amounts	Small amounts
NaOH	Small amounts	Small amounts

Exact potency of coagulant and antithrombotic proteins are listed on the carton



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Kcentra (prothrombin complex concentrate human) [prescribing information], Kankakee, IL; CSL Behring; October 2018.

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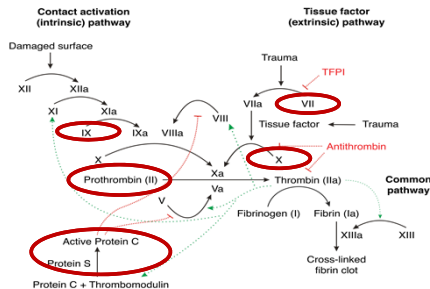
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## Mechanism of Action



<https://step1.medbullets.com/hematology/111004/coagulation-cascade>



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## Dosing of Kcentra<sup>®</sup>

INR Range	Dose
<b>VKA reversal with acute major bleeding or need for surgery or invasive procedure</b> Repeat dosing not recommended	
2 – <4	25 units/kg; max 2500 units
4 – 6	35 units/kg; max 3500 units
>6	50 units/kg; max 5000 units
<b>Life-threatening hemorrhage not associated with VKA (off-label)</b>	
Independent of INR	50 units/kg Additional 25 units/kg if clinically necessary

- Dosing approved for reversal of VKA anticoagulation in **adults**
- No labeled pediatric dosing available
- Should administer vitamin K concurrently



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Kcentra (prothrombin complex concentrate human) [prescribing information], Kankakee, IL; CSL Behring; October 2018.

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## PK/PD

- **Onset of Action:** Rapid, INR decline within 10 minutes
- **Duration:** 6 – 8 hours
- **Half-life elimination:**

Factor II: 48-60 hours	Factor VII: 1.5-6 hours
Factor IX: 20-24 hours	Factor X: 24-48 hours
Protein C: 1.5-6 hours	Protein S: 24-48 hours
- May be significantly reduced in severe hepatocellular damage, disseminated intravascular coagulation, or extended catabolic metabolism.

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## Monitoring

- INR at baseline and **30 minutes post dose**
- PT, hemoglobin and hematocrit to assess control of bleeding
- Vital signs, cardiac and CNS status during and post-infusion

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## Original Approval Study

- **Goal:**
  - Compare PCC (Beriplex®, Kcentra® or Confidex®) with plasma for urgent vitamin k antagonist (VKA) reversal in patients needing urgent surgical or invasive procedures
- **Inclusion:**
  - Inclusion: INR  $\geq 2.0$  receiving VKA therapy and needing urgent surgical procedure within 24hrs
  - Exclusion: Procedure for which an accurate estimated blood loss not possible (ruptured aneurysm or trauma)

Baseline INR	$\geq 2-4$	4-6	$>6$
PCC dose	25 units/kg	35 units/kg	50 units/kg
Plasma dose	10 mL/kg	12 mL/kg	15 mL/kg

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## Original Approval Study

**Primary endpoint: hemostasis during urgent surgical procedures**

- 78 (90%) of patients in PCC group vs 61(75%) in plasma group (treatment difference 14.3%, p=0.0142)


**Co-primary endpoint: rapid INR reduction (INR  $\leq$ 1.3 0.5h after end of infusion)**

- 48 (55%) of patients in PCC group vs 8 (10%) of patients in plasma group (treatment difference 45.3%, p<0.001; non-inferiority and superiority)

**Conclusion**

- PCC is non-inferior and superior to plasma for rapid INR reversal and effective hemostasis in patients needing VKA reversal for urgent surgical or invasive procedures

Goldstein JN. Lancet. 2015;35:2077-87.



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## PCC Dosing– Off Label

- European Heart Rhythm Association
  - For **life-threatening hemorrhage** associated with **non-vitamin K antagonist anticoagulation**
  - 50 units/kg
    - Additional 25 units/kg if necessary
  - Very limited evidence

Heidbuchel H. Europace. 2015 (10):1467-507



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## Kcentra® Dosing- Off Label

- Neurocritical Care Society/Society of Critical Care Medicine

**Intracranial hemorrhage (ICH) due to various antithrombotic agents**

<p style="text-align: center; font-size: small;">Oral direct factor Xa inhibitor-mediated: 50 units/kg</p>	<p style="text-align: center; font-size: small;">Direct thrombin inhibitor-mediated: 50 units/kg</p>	
<p style="font-size: x-small;">Give if ICH occurred within 3-5 half-lives of drug exposure or when liver failure co-exists</p>	<p style="font-size: x-small;">Give if ICH occurred within 3-5 half-lives of drug exposure</p>	<p style="font-size: x-small;">Ensure no evidence of renal failure or renal impairment leading to drug exposure beyond 3-5 half-lives</p>

Frerking JA. Neurocrit Care 2016 (1):6-46



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## Coagulopathy in Trauma

Cause of acute trauma of coagulopathy (ATC)	<ul style="list-style-type: none"> <li>Hemorrhage</li> <li>Secondary effect of trauma</li> </ul>
Hemostatic resuscitation	<ul style="list-style-type: none"> <li>Massive transfusion protocol</li> <li>FFP, platelets, PRBC</li> </ul>
Complications associated with resuscitation	<ul style="list-style-type: none"> <li>Volume overload</li> <li>Infection</li> <li>Transfusion related reaction</li> </ul>
PCC Advantages	<ul style="list-style-type: none"> <li>Smaller volume infused</li> <li>Faster INR reduction</li> <li>Less infusion related adverse effects</li> </ul>

Matsushima K. *Ann J Surg.* 2015 (2):413-7

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## Guideline Recommended Vitamin K Deficiency Bleeding

- Non-life-threatening: 250-300 mcg/kg IV vitamin K (usually 1-2 mg)
- Life-threatening hemorrhage or emergent surgical intervention use one of the following plus vitamin K:
  - FFP
  - Recombinant factor VIIa
  - PCC

**“The use of PCC should be considered in the presence of life-threatening hemorrhage or intracranial hemorrhage when it is necessary to normalize the levels of depleted coagulation factors. Extrapolation of adults studies suggest a dose of 50 units/kg.”**

Williams MD. *Br J Haematol.* 2002; 119:295-309

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## Objectives

Determine potential indications for use of Kcentra® in the pediatric population

Assess Kcentra®'s role in therapy based on literature and guidelines

Develop a treatment plan using Kcentra® for a patient case

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## Kcentra® in Trauma

<b>Aim</b>	Compare the outcomes in coagulopathy trauma patients <b>receiving Kcentra® + FFP versus FFP alone.</b>
<b>Methods</b>	-Retrospective analysis of database of coagulopathic <b>trauma patients</b> - <b>Inclusion:</b> <b>age ≥18 years</b> , trauma patient, admission INR ≥1.5, received <b>Kcentra® +FFP or FFP alone</b> - <b>Exclusion:</b> Documented bleeding disorder, chronic liver disease, on preinjury anticoagulant, died in the ED, received Kcentra® without FFP
<b>Dosing</b>	-Utilized <b>Kcentra® 25 units/kg</b> , given based on discretion of trauma surgeon; FFP administered as part of massive transfusion protocol
<b>Outcomes</b>	- <b>Primary:</b> INR correction, time and rate of correction, blood and blood product use, and thromboembolic complications - <b>Secondary:</b> hospital length of stay, ICU length of stay, and mortality

 Jehan F et al. J Trauma Acute Care Surg. 2018; 85(1):18-24.  
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## Kcentra® in Trauma

Characteristics	Kcentra® +FFP (n=40)	FFP (n=80)	P-value
Age: mean ± SD, y	57 ± 20.9	58 ± 19	0.91
Blunt injury, % (n)	83% (33)	87% (69)	0.76
Antiplatelet use, % (n)	25% (10)	26.5% (21)	0.35
GCS, median [IQR]	10 [3-13]	10 [3-12]	0.21
Mechanism of injury, %(n)			
MVC	40% (16)	39% (31)	0.85
Pedestrian struck	35% (14)	33% (26)	0.63
Falls	12% (5)	16% (13)	0.25
Hematologic parameters			
Initial hemoglobin	13 ± 3	12 ± 4	0.13
Initial INR	1.9 ± 2	1.8 ± 2	0.15
TXA, % (n)	58% (23)	52% (42)	0.34
Surgical intervention, % (n)	28% (11)	26% (21)	1.00

 Jehan F et al. J Trauma Acute Care Surg. 2018; 85(1):18-24.  
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## Kcentra® in Trauma

Variables	Kcentra® + FFP (n=40)	FFP (n=80)	p
<b>Primary Outcomes</b>			
<b>INR</b>			
Time to correction, min	373 ± 211	955 ± 524	0.001
Correction of INR, %(n)	95% (38)	92% (74)	0.62
Rate of INR correction	0.31 ± 0.1	0.08 ± 0.1	0.01
<b>Blood products</b>			
pRBC transfused, units	7 ± 3	9 ± 5	0.04
FFP, units	5 ± 2	7 ± 3	0.03
Platelets, units	3 ± 3	3 ± 3	0.72
<b>Thromboembolic complications</b>			
DVT	2.5% (1)	1.2% (1)	0.51
PE	0%	0%	0.95
Mesenteric infarction	0%	1.2% (1)	0.84
<b>Secondary Outcomes</b>			
ICU length of stay	1 [1-2]	1 [1-2]	0.91
Hospital length of stay (days)	5 [2-6]	7 [3-8]	0.03
<b>Mortality</b>	25% (10)	33% (26)	0.04

 Jehan F et al. J Trauma Acute Care Surg. 2018; 85(1):18-24.  
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## Kcentra® in Trauma

- The use of Kcentra® + FFP for reversal of coagulopathy of trauma is associated with decreased time to correction of INR, blood products transfused, and mortality
- No increase in thromboembolic complications compared to FFP alone
- First to report superiority of Kcentra® + FFP compared with FFP alone in coagulopathy of trauma


 Jehan F et al. J Trauma Acute Care Surg. 2018; 85(1):18-24.  
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## Pediatric Patient on Warfarin

- Case report
- Administration of Kcentra® in a 9 YOF who presented with acute bleeding, **elevated INR secondary to warfarin**
- HPI: tachycardia (122 beats/min), GCS 15, new somnolence and headache
- CT **revealed intratumoral hemorrhage** with intraventricular extension and hydrocephalus
- Medication history:
  - Warfarin for DVT
  - INR 1.9, **warfarin increased from 7.5 mg daily to 10 mg daily**; enoxaparin started as a bridge
  - Received warfarin night prior to and enoxaparin morning of presentation


 Adams CB et al. Am J Emerg Med. 2016; 34(8):1182.e1-2  
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## Pediatric Patient on Warfarin

- Current labs:
  - **INR 3.3**, PT and aPTT elevated at 35.4s and 65.7s
- Treatment:
  - Protamine sulfate 50 mg IV for attempted enoxaparin reversal
  - **Vitamin K 5 mg IV + Kcentra® 1192 U (21.8 units/kg) IV**
- Outcome:
  - **60 min after Kcentra®** and 85 minutes after protamine:
    - INR 1.2, PT 12.5s, aPTT 35.8s, anti-factor Xa level 0.5 u/mL
  - **20 hours after administration**:
    - INR 1.4, anti-factor Xa 0 U/mL
  - Death 36 hours after initial presentation due to deteriorating clinical status and decision for comfort measures


 Adams CB et al. Am J Emerg Med. 2016; 34(8):1182.e1-2  
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## Lack of Vitamin K Prophylaxis

- Case report of infant with no vitamin k supplementation at birth
- 6 week old, full term, previously healthy, breast fed female infant
- Presents with AMS, Tmax 100.3°F followed by lethargy, ↓ PO intake, posturing and dilated, non-reactive pupils
- *CT showed left temporal parenchymal hemorrhage, 2 right parietal parenchymal hemorrhages, right parietal subdural hematoma, left cranial fossa subdural hematoma, scattered subarachnoid blood and diffuse edema*
- Labs:
  - INR >10, PT 150 seconds
  - Hemoglobin 5.2 g/dL, hematocrit 15.4%



Rech MA et al. J Pediatr. 2015;167:1443-4.

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## Lack of Vitamin K Prophylaxis

- Medications given:
  - Kcentra® 50 units/kg for reversal of coagulopathy
  - FFP 70 mL while waiting for Kcentra®
  - Vitamin K 5 mg IV
  - PRBC
- Outcomes:
  - Before vitamin K administration INR went from 10>>1.3
  - After correction of coagulopathy, repeat head CT stable
  - Usual traumatic brain injury measures initiated
  - MRI on day 3 demonstrated ischemia of medial left thalamus, right frontal, right parietal, and right and left temporal lobes. MRI on day 6 stable
  - DVT diagnosed on day 4, thought to be associated with central venous catheter
  - Discharged home on hospital day 10



Rech MA et al. J Pediatr. 2015;167:1443-4.

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## Pediatric Case Series

- Retrospective case series over 5 year period
- Inclusion:
  - Any pediatric patient (neonate-16 years) who had received Octaplex® or Beriplex® at Stollery Children's hospital
- Utilized transfusion medicine database
  - Age, dose, 30 day follow up of thromboembolic complications, vitamin K co-administration or other blood product
  - Chart review performed for any additional information
- Dosing strategy:

Patient weight	INR <3.0	INR >3.0
<10 kg	10 mL (250 units)	20 mL (500 units)
10-25 kg	20 mL (500 units)	30 mL (750 units)
25-50 kg	30 mL (750 units)	40 mL (1000 units)



Noga T et al. Vox Sanguinis. 2016;110:253-57.

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## Pediatric Case Series

- 16 patients received a **single dose of Octaplex® or Beriplex®**
- Age range 23 days-16 years
- 11 patients received for VKA reversal, 2 patients received prior to cardiac surgery for elevated INR unrelated to VKA, 3 patients received for post cardiopulmonary bypass bleeding
- 82% of patients for VKA reversal demonstrated rapid improvements in INRs
  - In 64% of patients INR improved to clinical target range (1.2-1.6)
- **1 patient with a DVT**
  - Left internal jugular and innominate vein occlusion one day post-op/post PCC dose in 4 year old male

Noga T et al. Vox Sanguinis. 2016;110:253-57.



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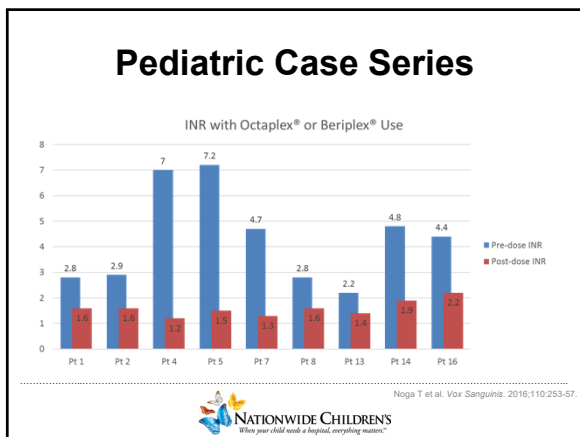
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## Pediatric Patient Review

- 17 patient review over 6 month period
  - All patients received other hemostatic medications or blood products around the same time as Kcentra®

Baseline Characteristics and Reason for Use (n=17)		
Age, n (%)	Neonate (<31 days)	3 (18%)
	Infant (1 year of age)	3 (18%)
	Child (1-12 years of age)	6 (35%)
	Adolescent (13-18 years of age)	3 (18%)
	Adults (>18 years of age)	2 (12%)
Reason for Kcentra® use; resolution of symptoms	Bleeding	12 (71%); 6 (50%)
Abnormal coagulation panel & history of bleeding/bruising	Warfarin related bleeding	3 (18%); 3 (100%)
		2 (12%); 1 (50%)

Beatty et al. Annals of Pharmacotherapy. 2016;50(1):70-71.



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## Pediatric Case Series

- Prior to Kcentra®
  - Majority of patients received FFP (71%), blood products (100%), PRBC (59%)
  - Some patients received cryoprecipitate (41%), platelets (47%), antifibrinolytics (12%) and vitamin K (35%)
- After Kcentra®
  - Blood products (77%), FFP (59%), platelets (47%), PRBC (47%), vitamin K (24%), cryoprecipitate (18%)

Summary of Patient Data (n=17)	
<b>Underlying Disorder</b>	
Liver and/or multisystem organ failure	7 (42%)
Malignancy	2 (12%)
Congenital heart disease	2 (12%)
Other	6 (35%)
<b>INR (prior to Kcentra)</b>	
<2	6 (35%)
2-5	10 (59%)
>5	1 (6%)
<b>Patients received multiple doses of Kcentra</b>	
Yes	7 (41%)
No	10 (59%)

Beatty et al. Annals of Pharmacotherapy. 2016;50(1):70-71.

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## Pediatric Case Series

- 6 (50%) of the 12 patients with active bleeding and 1 (50%) of the 2 patients with warfarin related bleeding had initial and/or complete cessation of bleeding after Kcentra®
  - The 6 patients who continued to **bleed received less than 25 units/kg**, 2 had liver failure
- **Doses ranged from 10-50 units/kg**
- One patient with CRRT circuit thrombosis
  - 11 doses of Kcentra®, 4 prior to event
  - **No other thrombotic events identified**

Beatty et al. Annals of Pharmacotherapy. 2016;50(1):70-71.

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## Kcentra® Role in Trauma?

Study	Non-VKA patients?	Dose of Kcentra®	Other medications? (FFP, Vit K, etc)	Thromboembolic events
Goldstein et al	No	25-50 units/kg	Vit K	7% of patients
Jehan et al	Yes	25 units/kg	FFP	2.5% of patients
Adams et al	No	25 units/kg	Vit K, protamine	Unknown
Rech et al	Yes	50 units/kg	FFP, vit K	DVT
Noga et al	Yes	15-75 units/kg	Vit K	1 pt (6.25%)
Beatty et al	Yes	10-50 units/kg	Multiple	1 pt (5.9%)

Beatty et al. Annals of Pharmacotherapy. 2016;50(1):70-71.

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## Future Directions

- All studies and cases showed a decrease in INR with PCC use
- Based on a small cohort of pediatric patients studied, thromboembolic events may not occur frequently
- Questions that still need answered:
  - Patient outcomes
    - PICU length of stay
    - Morbidity and mortality
    - Time to surgery
- Retrospective studies needed



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## Objectives

- Determine potential indications for use of Kcentra® in the pediatric population
- Assess Kcentra®'s role in therapy based on literature and guidelines
- Develop a treatment plan using Kcentra® for a patient case



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## Patient Case

6 YOM (wt = 20 kg) in an MVC rollover arrives as a level I trauma, CT shows large SDH and cerebral edema. Neurosurgery would like to go to the OR for a craniectomy but INR is 2.5.

Trauma attending is inquiring about the use of Kcentra®. What would you recommend?



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### Patient Case

- a. Do not recommend, not enough pediatric information
- b. Recommend Kcentra® 25 units/kg based on INR
- c. Recommend Kcentra® 50 units/kg based on life-threatening hemorrhage
- d. Recommend other blood products: i.e. FFP, pRBC and recheck INR in 1 hour



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### Kcentra® use in a pediatric hospital



7 Patients received Kcentra®

- June 2017 – June 2018
- 1 patient on VKA
- 2 patients > 18 years old

10 additional patients

- Since initial chart review



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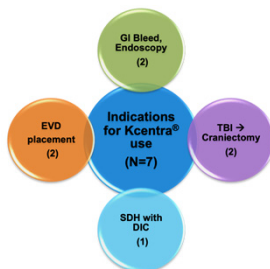
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### PCC Indications



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## Kcentra® Dosing Guidelines

INR Range	Dose
<b>VKA reversal with acute major bleeding or need for surgery or invasive procedure</b> Repeat dosing not recommended	
2 – <4	25 units/kg; max 2500 units
4 – 6	35 units/kg; max 3500 units
>6	50 units/kg; max 5000 units
<b>Life-threatening hemorrhage not associated with VKA (off-label)</b>	
Independent of INR	50 units/kg Additional 25 units/kg if clinically necessary



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Kcentra (prothrombin complex concentrate human) [prescribing information]  
Europe, 2015 (10);1487-507

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## Kcentra® Dosing

Patient #	Age	Initial INR	PCC dose units/kg	Time from dose to INR (minutes)	Indication
1	15	2	25	206	TBI → EVD
		1.41*	25	44	
2	2	5.72	37.1	53	SDH, DIC
3	18	4.58	28.5	68	GI bleed → Endoscopy
4	17	1.84	25.5	117	EVD
5	3	2.32	29.4	218	TBI → Craniectomy
6	5	2.23	50	70	TBI → Craniectomy
7	22	5.91	35.6	122	GI bleed → Endoscopy
Average**		3.51	33	122	

\*INR prior to 2<sup>nd</sup> dose  
\*\*Averages calculated only based on initial doses



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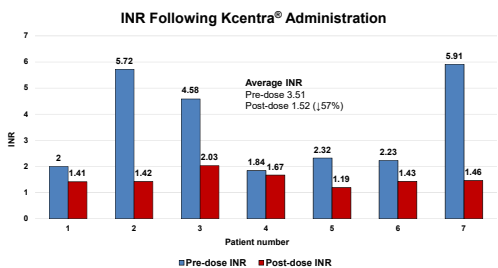
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## Outcomes



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## Adjunctive Agents

- All patients received vitamin K
- Most patients received a combination of:
  - pRBCs
  - FFP
  - Platelets
  - Cryoprecipitate



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## Outcomes

INR Reduction


- Average reduction by 2 (↓ 57%)
- Cessation of GI bleed or allowed procedure
- Unknown how much Kcentra® influenced INR independently
- Future directions → Vitamin K alone vs Kcentra® + Vitamin K

INR Recheck

- Average time to recheck → 2 hours, recommended 30 minutes
- Could procedures occurred earlier?
- Pharmacist involvement with ordering labs → INR checks

Adverse effects

- No thrombosis or other adverse effects noted
- Many patients were severe traumas
- 57% mortality rate



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## Items to Consider

- Availability
  - Kcentra® only in US
    - 500 units
    - 1000 units
  - Canada
    - Beriplex
    - Octaplex
- Cost
  - \$2.90 per unit\*

- Restrictions
  - None currently
  - Possibilities
    - INR
    - Patient severity
    - Services
    - Procedure





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### Patient Case

6 YOM (wt = 20 kg) in an MVC rollover arrives as a level I trauma, CT shows large SDH and cerebral edema. Neurosurgery would like to go to the OR for a craniectomy but INR is 2.5.

Trauma attending is inquiring about the use of Kcentra®. What would you recommend?

- b. Recommend Kcentra® 25 units/kg based on INR
- c. Recommend Kcentra® 50 units/kg based on life-threatening hemorrhage



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### Conclusion

- Kcentra® may offer benefit to the pediatric population in indications such as ATC and vitamin K deficiency bleeding
- Available pediatric data appears promising, but a lack of outcome data to determine true benefit remains
- Kcentra® has shown to decrease INR quickly to allow for urgent procedures or bleeding cessation



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### Questions



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**Race for INR Reduction:  
Review of prothrombin  
complex concentrate  
(PCC) use in a  
pediatric hospital**



Krista Dumkow, PharmD Candidate  
Katelyn Bull, PharmD  
Jenny Steinbrenner, PharmD, BCPPS



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