UPDATE OF NEUROCRITICAL CARE PHARMACOTHERAPY

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DISCLOSURE STATEMENT OF FINANCIAL INTEREST

I, Vera Wilson, do not have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

DISCLOSURE STATEMENT OF UNAPPROVED/INVESTIGATIVE USE

I, Vera Wilson, do anticipate discussing the unapproved/investigative use of a commercial product during this presentation.
OBJECTIVES

- Describe emergent reversal options of warfarin and target-specific oral anticoagulants for life-threatening bleeding
- Identify contraindications and precautions to ketamine administration
- Recognize evidence-based treatment options and their dosing for elevated intracranial pressure
- Develop monitoring plans for mannitol and hypertonic saline use

EMERGENT REVERSAL OPTIONS OF WARFARIN AND TARGET-SPECIFIC ORAL ANTICOAGULANTS FOR LIFE-THREATENING BLEEDING

MECHANISM OF ACTION

- Anticoag chart w/ where warfarin and TSOAs exert their effect
NON-ACTIVATED FOUR FACTOR PROTHROMBIN COMPLEX CONCENTRATE (4F-PCC)

- Indicated for urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonist (VKA) [e.g. warfarin] therapy in adult patients with acute major bleeding or need urgent surgery/invasive procedure
- Requires individualized dosing based on patient’s baseline INR and body weight
- Administer vitamin K concurrently to maintain factor levels once the effects of 4F-PCC have diminished
- Repeat dosing of 4F-PCC is not recommended

4F-PCC BOXED WARNING

- Both fatal and non-fatal arterial and venous thromboembolic complications have been reported
- Weigh potential benefits of VKA reversal vs. potential risks of thromboembolic events
- Not studied in patients who had a thromboembolic event, MI, disseminated intravascular coagulation (DIC), CVA, TIA, unstable angina or severe PVD within the prior 3 months
- May not be suitable in patients with thromboembolic events in the prior 3 months

4F-PCC CONTRAINDICATIONS

- Known anaphylactic or severe systemic reactions to 4F-PCC or any components in 4F-PCC (including heparin, Factor II, VII, IX, X, Proteins C and S, Antithrombin III and human albumin)
- DIC
- Known heparin-induced thrombocytopenia
### 4F-PCC DOSING

<table>
<thead>
<tr>
<th>Pre-treatment INR</th>
<th>2 – 3.9</th>
<th>4 – 6</th>
<th>Greater than 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>4F-PCC dose* (units/kg)</td>
<td>25</td>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td>Maximum dose* (units)</td>
<td>Not to exceed 2500</td>
<td>Not to exceed 3500</td>
<td>Not to exceed 5000</td>
</tr>
</tbody>
</table>

*Dose is per units of Factor IX


### 4F-PCC VERSUS FRESH FROZEN PLASMA (FFP)

<table>
<thead>
<tr>
<th>4F-PCC</th>
<th>FFP</th>
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<tbody>
<tr>
<td>Quick onset of action</td>
<td>Quick onset of action</td>
</tr>
<tr>
<td>Less volume</td>
<td>Larger volume</td>
</tr>
<tr>
<td>Short infusion time</td>
<td>Longer infusion time</td>
</tr>
<tr>
<td>Risk of transmitting infectious agents and thromboembolism</td>
<td>Risk of transmitting infectious agents and thromboembolism</td>
</tr>
<tr>
<td>Expensive</td>
<td>Inexpensive</td>
</tr>
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</table>


### MANAGEMENT OF ELEVATED INR FROM VKA

<table>
<thead>
<tr>
<th>INR &amp; Patient Situation</th>
<th>Recommendation</th>
<th>Grade of Evidence</th>
</tr>
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</table>
| VKA-associated major bleeding | -Suggest rapid reversal of anticoagulation with four-factor PCC rather than with plasma  
-Suggest the additional use of vitamin K 5-10mg administered by slow IV injection rather than reversal with coagulation factors alone | Grade 2C |
SUMMARY OF CHEST RECOMMENDATIONS

- Recommendations from 2012 Chest Guidelines for management of elevated INRs from VKAs are considered "weak recommendations"
- FFP disadvantages include preparation time and higher volume (potential for volume overload)
- Regardless of which option is used (FFP or PCC) for VKA-associated major bleeding, it must be used with vitamin K 5 - 10 mg IV infusion

EFFICACY AND SAFETY OF 4F-PCC FOR VKA REVERSAL IN ACUTE MAJOR BLEEDING

- Included patients ≥18 years old receiving VKA therapy with an elevated INR and experiencing acute major bleeding
- Treatment with either 4F-PCC vs. plasma
- Effective hemostasis was 72.4% in the 4F-PCC group vs. 66.4% in the plasma group (95% CI 1.8 – 19.9)
- Rapid INR reduction (INR ≤ 1.3 at 0.5 hour after the end of infusion)
  - 61 patients (62.2%) in the 4F-PCC group vs. 10 (9.6%) in the plasma group
  - Difference demonstrated superiority of 4F-PCC over plasma (difference, 52.6% [39.4 to 65.9])
- Thromboembolic AE occurred 7.8% 4F-PCC group vs. 6.4% plasma group

4F-PCC VS. PLASMA FOR URGENT REVERSAL IN SURGERY OR INVASIVE INTERVENTIONS

- Included patients ≥18 years old needing rapid VKA reversal prior to urgent surgical or invasive procedure
- Demonstrated both non-inferiority and superiority of 4F-PCC over plasma (difference 14.3%, 95% CI 2.8 – 25.8) for effective hemostasis
- Non-inferiority and superiority achieved for rapid INR reduction (≤1.3 at 0.5 h after infusion end) of 4F-PCC over plasma (difference 45.3%, 95% CI 31.9 – 56.4)
ADVERSE EVENTS

• Thromboembolic events (p=0.77)
  • 6 (7%) patients in 4F-PCC group
  • 7 (8%) patients in plasma group
• Fluid overload or similar cardiac events (p<0.05)
  • 3 (3%) patients in 4F-PCC group
  • 11 (13%) patients in plasma group

IDARUCIZUMAB FOR DABIGATRAN REVERSAL

- RE-VERSE AD (Reversal Effects of Idarucizumab on Active Dabigatran)
  - Ongoing, multicenter, prospective cohort which included adult patient taking dabigatran who had:
    - Overt, uncontrollable or life-threatening bleeding that required a reversal agent (Group A, N=51)
    - Required surgery or other invasive procedures that could not be delayed for at least 6 hours and required normal hemostasis (Group B, N=39)
  - Patients received idarucizumab 5 mg infusions

RE-VERSE AD STUDY

- Primary endpoint – at 12 hours and 24 hours
  - Dilute thrombin time was below the ULN of the normal range for 90% in group A and 81% group B
  - Ecarin clotting time was below the ULN of the normal range for 72% in group A and 54% group B
  - Group A – median investigator-reported time to cessation of bleeding in 11.4 hours
  - Group B – normal intraoperative hemostasis in 92%
  - Thrombotic events occurred in 5 patients
  - 18 patients died
  - Ongoing phase III study with patients currently being enrolled

REVERSAL FACTOR XA INHIBITORS
BRAIN TRAUMA FOUNDATION (BTF) GUIDELINE RECOMMENDATIONS FOR SEVERE TBI

- Mannitol effective for control of raised ICP (Level II)
  - Doses 0.25 – 1 g/kg
  - Avoid arterial hypotension (SBP<90)
- Restrict mannitol use prior to ICP monitoring to patients with (Level III):
  - Signs of transtentorial herniation
  - Progressive neurological deterioration not attributable to extracranial causes

J Neurotrauma. 2007; 24(suppl1):S1-95.

BTF GUIDELINE RECOMMENDATIONS FOR HYPERTONIC SALINE (HS) USE IN SEVERE TBI

- No graded recommendations for use of HS
- Studies included suggest that HS as a bolus may be effective adjuvant or alternative to mannitol
- Guidelines are dated (2007)

J Neurotrauma. 2007; 24(suppl1):S1-95.

HYPERTONIC SALINE

- General info
- Monitoring
MANNITOL

- General info
- Monitoring

HIDDEN SLIDE SECTION

INFUSION DETAILS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>4F-PCC (n=50)</th>
<th>Plasma (n=104)</th>
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<tbody>
<tr>
<td>Study product*</td>
<td></td>
<td></td>
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<tr>
<td>Duration, median (range), min</td>
<td>17.0 (7-288)</td>
<td>148.0 (28-928)</td>
</tr>
<tr>
<td>Total volume, median (range), mL</td>
<td>90.4 (50-230)</td>
<td>813.5 (400-1523)</td>
</tr>
<tr>
<td>Infusion rate, median (range), ml/min</td>
<td>154.1 (7.3-297.1)</td>
<td>8.0 (1.1-38.6)</td>
</tr>
<tr>
<td>for 4F-PCC, ml/min for plasma</td>
<td></td>
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<tr>
<td>Packed red blood cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients receiving ≥1 transfusion, n (%)</td>
<td>46 (48.0)</td>
<td>47 (45.2)</td>
</tr>
<tr>
<td>Units transfused, mean (SD)</td>
<td>1.4 (1.77)</td>
<td>1.2 (1.57)</td>
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4F-PCC indicates 4-factor prothrombin complex concentrate.
*The patient randomized to 4F-PCC who received plasma was excluded.