Pharmacy and Therapeutics Committee:

Dear Drs., Pharmacists, RNs etc.:

I am writing to you asking that you open a discussion and approve the usage of “4 factor” Prothrombin Complex Concentrate (PCC) for several utilizations:

1. Reversal of Coumadin/warfarin in all surgeries or invasive procedures wherein time for vitamin K to work is not possible. PCC should replace the use of FFP (a dangerous therapy)
2. Use in bleeding post cardiopulmonary bypass patients with diffuse capillary oozing (to be defined herein) and/or defined coagulopathy by STAT coagulation testing (see attached algorithm)
3. Reversal of warfarin/Coumadin for surgical patients wherein vitamin K cannot be utilized due to time (less than 12-24 hours)- bleeding in trauma and neurosurgery when the algorithm is used.
4. Reversal of the NOACS- oral anti-Xa and direct thrombin inhibitors when invasive procedures are planned or bleeding after invasive procedures wherein these agents had been taken.

I was recruited one year ago to come to UF to bring Patient Blood Management (PBM) and to make UF the poster child for best practice. Blood transfusion has been shown to be associated with increased morbidity and mortality. Red blood cell transfusions are immunosuppressive, but where PCC plays into the larger program for PBM is in helping to radically reduce the use of FFP. FFP usage at UF is dramatically higher than at similar institutions around the country and far below the leaders in PBM. When the state of Virginia cardiac surgery programs adopted PBM, including using coagulation treatment algorithms and reducing FFP by using PCC morbidity and mortality dropped, length of time in ICU and ventilation complications dropped. Rather than costing more money this change saved the State of Virginia $49,000,000.00.

I will make the case to you that FFP is no longer an acceptable routine methodology for treatment/reversal of coagulation dysfunction in these above indications.

You will find extensive literature attached regarding the risks of FFP in terms of Transfusion Related Acute Lung Injury (TRALI), possible TRALI (pTRALI), and Transfusion Associated Cardiac Overload (TACO). TRALI is now regarded by the FDA and the CDC as the most common cause of death related to blood product infusion. Debate goes on in the academic literature regarding the incidence of TRALI. In discussing TRALI one must realize that it is a diagnosis created by the blood banking community and is a diagnosis of exclusion- meaning that TRALI cannot be called TRALI unless there are no other risks or reasons for why a patient might undergo acute lung decompensation. So now the “politically correct” definition of pTRALI has been coined.

The incidence of TRALI in cardiac surgery is thought to be between 1.2-8% for all comers who are transfused at heart surgery. The Mayo Clinic has done extensive work prospectively and has found the incidence to be 1.2% for TRALI in heart surgery and the Cleveland Clinic found … . Those that get TRALI have a 50% mortality. TACO occurs in 1-10% of all transfused patients (red cells, FFP and platelets) with up to a 30% mortality (heart surgery patients). In non-cardiac patients the incidence is thought to be 3-5.5% (twice the LOS, 3 times as long mechanical ventilation, and twice the mortality). TACO was responsible for 22% of all transfusion fatalities in the United States in 2013-14 and 55% of all deaths in the United Kingdom Hemo-vigilance system (2013). Recently a 53,139 patient review of patients having non-cardiac surgery at the Mayo Clinic showed the incidence at 3.8%. These data show the complication is neither rare nor predictable. Therefore FFP cannot be considered a “gold standard” but must be considered a risky and unproven therapeutic intervention whose time has come to be phased out for most utilizations (trauma may yet be an indication- for other reasons).

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FFP is unproven in that there is no cogent literature showing that FFP usage for reversal of warfarin/Coumadin decreases surgical bleeding. Indeed the FDA and the Cochrane Index have stated that FFP does not have an indication that prophylactically reduces bleeding. In heart surgery it is actually associated with increased bleeding as well as the other effects noted.

PCC is approved for the reversal of anti-coagulation from vitamin K dependent drug treatments- Coumadin/warfarin. It is now accepted by many institutions that PCC is the preferred method of reversal of anti-coagulation-not FFP. Vitamin K should still be utilized where time is enough for the agent to work. But if immediate, urgent or emergent invasive /surgical interventions are required PCC should be the go to modality- not FFP!

I have included a number of references wherein PCC has been tested prospectively (you cannot do double blind) versus FFP in bleeding after heart surgery, neurosurgery and trauma. In heart surgery PCC use in left ventricular assist devices (with brain bleeds), heart transplantation and especially when thrombin generation function is assessed have been quite useful.

As part of our PBM program here we will be refining, educating and implementing the coagulation treatment algorithm based upon the work of Keyvan Kakouti et al, from the University of Toronto. I would point out that I have personally been involved with these treatment algorithms as they have evolved in Europe, Canada and the United States. It will take some time to get buy in, train and have surgeons, anesthesiologists, critical care doctors and others comfortable with the coagulation algorithm. That being said, having PCC available and part of the treatment availability is vitally important to improved outcome by beginning to reduce the use of FFP. Remember again, although FFP is relatively inexpensive per unit, it carries an unacceptable high risk for TRALI and TACO. In the prospective literature wherein PCC was used versus FFP PCC proved less expensive.

We today have factor VIIa approved for severe intractable bleeding in heart surgery. By putting sanity and science into the decision tree we anticipate almost complete abolition of factor VIIa usage. Although PCC may be utilized in 2-5% of cases (my estimation) a reduction in bleeding, other blood product utilization, length of hospital stay and ICU complications will improve cost effectiveness for the whole institution. We are here to take care of the whole patient and cost effectiveness has to be looked at as total UF/Shands patient experience. As a world’s expert in blood transfusion, coagulation and patient blood management this approval is key to the PBM program. If I were a patient here, I certainly would not like to have received FFP when a drug- PCC was available-especially if my lungs failed after being given FFP.

I look forward to presenting this somewhat complex series of issues, review the literature with you/your committee and discuss the details. Please let me know when and where to appear to the entire committee.

Sincerely yours,

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