Factor Concentrates.
More is better?

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Scenario -1

- Call from OR !
- Patients is bleeding out **!**
- Don’t’ ask why, what rate what’s been done**!**
- We need blood now !
- What kind of blood would that be ?
- Just Everything **!!!**

Wrong Scenario

- Why in this day and age do medical professionals have such a poor understanding of blood and blood products?
- Whose job is it to decide what is the most appropriate therapy **?**
- **Answer – he who controls the product. !!!**

Needed Background Information

- Was the patient normal before surgery.
- Did he have any underlying coagulopathy ? Liver disease !
- Did he have any drugs that inhibit platelet function ?
- Do you have any recent labs !

Management of Bleeding

- Most bleeding that occurs in hospitalised patients is not anticipated, but is because of what we do to them !
- Predictable bleeding patients such as hemophilia (factors VIII, IX and XI) & Von Willebrand's disease are very different.

The Hemophilias

- Factor VIII & XI deficiency is limited to about 30-40,000 male patients in the US, with most about 30K being F VIII.
- Factor XI deficiency occurs almost exclusively in Askanazi Jews & is rare outside Israel.

Hemophilia Treatment

- Focused on replacing the missing factor by purified or recombinant specific Factor.
- Patients can treat themselves at home for small bleeds.
- For surgery, will need hopsitaisation and prolonged treatment (usually 10-14days) till wound heals.

Hemophilia Problems

- About 25 % of them will develop an antibody /inhibitor to the transfused material recognising it as “foreign”
- They can be very difficult and expensive to treat.
- Specific strategies have been developed to “bypass” or hyperactivated the clotting system.

Hemophilia Treatments

- Human and recombinant F VIII and Factor IX are widely available.
- Factor IX concentrate available in Israel.
- All work predictably.
- Formation of inhibitors is only marginally less with recombinant products.

The Inhibitor Patient

- The blood banks worst financial nightmare!
- Inhibitor bypassing products include FEIBA and Autoplex.
- Exact mechanism of they work is not known, but thought to be focused through factor Xa.

Ultimate Inhibitor Patient

- Resistant to FVIII and bypassing products.
- Now use NovoSeven (rec. F VIIa)
- Doses of 90 -300µg/kg are required every 2 hours.
- This can cost up to $30,000 per dose in a 100kg male.
- This represents >$250, 000/day !!

Rarer Concentrates

- C1-esterase inhibitor concecnatre for patients with hereditary angioedema.
- Not FDA approved in US but is allowed in through Argentina for “off label use” through Angioedema Foundation.
- Used mainly for patients in high risk situations i.e pregnancy delivery

More Rarer Concentrates

- Protein C concentrate available for compassionate use in US for babies with homozygous Protein C deficiency.
- Can get life threatening thrombosis at birth if not treated.

Unique Concentrates

- Rec. Activated Protein C (Xigris)
- Specifically designed to prevent micro thrombi in the septic patient by inhibiting thrombin generation.
- Clinical trials highly successful, but poor utilisation in US, probably due to poor validation of bacterial sepsis & fear of “bleeding” from anticoagulant.

Different Concentrates

- Three plasma derived factor IX concentrates (Bebulin, Alphanine & ?) are in reality "PCCs"
- They contain not only FIX, but high does of F II & F X and low doses of F VII.
- Bebulin also contains Proteins C & S, making it very useful for acute reversal of Coumadin Overdose.

Oldies but Goodies

- Antithrombin concentrates have been available for 15 years as a plasma derived product, in this past year as transgenic material from goats milk.
- Developed specifically for the congenital AT deficient patient but useful also in acquired deficiency such as DIC and Liver Transplantation.

More Oldies but Goodies

- Fibrinogen Concentrates were approved recently in the US.
- They were available many years ago but were withdrawn because of there high viral disease transmission.
- New products are safe even though still plasma derived.
- Should prove very useful.

All Hail the New King !

- The mantra for most surgeons in a bleeding patient is it’s not their fault.
- If they are losing blood then give blood back !
- Problem is we don’t have blood any more, we have bits of blood.
- Surgeons and anesthesiologists don’t really know how to dose bits of blood

All Hail the New King !

- How much of a “bit to give” depends on who is shouting the most.
- The famous “just keep me 5 units ahead”
- Ahead of what !!
- Trauma protocols have developed good strategies that provide products in a balanced manner

All Hail the New King !

- Most blood product ordering is done without any real thought.
- The 2,2 and 1 (FFP, Cryo & platelets) is “routine” but not logical.
- If that does not work, give twice as much !!
- If it’s going to hell in a hand basket, order the “King of Clots” !!

The King is NovoSeven !!

- Recombinant FVIIa is the most potent hemostatic agent we have.
- It is not used at physiological dose but at pharmaceutical doses (20 x higher)
- It was not developed to plug holes in patients put there by surgeons.
- It is however effective used correctly.

More King

- It use needs to be controlled by transfusion medicine physicians who understand its benefits & limitations.
- It can and does cause thrombosis in off label use (new FDA Black Box Warning last week)
- Most of it's use in US is "off label"

Even More King

- It is very effective in long surgeries with a lot of tissue damage and exposure.
- Good examples are Aortic Aneurysms and Cardiac bypass.
- We allow 3 small 2mg doses to be given by defined Cardiac Anesthesia MD in a 24 hour period.

The King Again !

- It is not a panacea for all bleeding that is uncontrollable.
- More surgery is usually needed also.
- It needs to be give with an adequate level of Fibrinogen (> 100mg/dL).
- It can and does activate platelets.
- It can be truly life saving !

The Future

- More is not better .
- Use of the correct product will work better than loads of everything.
- Stuff rarely work .
- Some concentrates will recycle as anti-inflammatories with anticoagulant overtones (AT rec & rAPC).

More Future

- New unique concentrates will continue to be developed.
- Active site blocked r FVIIa.
- Genetically matched recombinant /human FVIII to prevent inhibitor.
- Plasmin as an antifibrinolytic (drug)
- Things you can’t imagine.