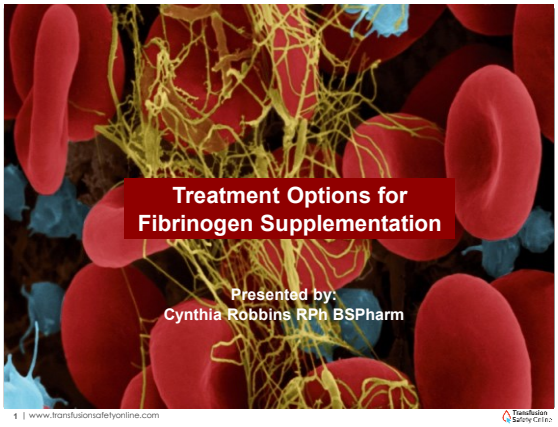





1

## About Your Speaker

***Cynthia Robbins RPhBSPharm***
*Sr. Director of Hospital Affairs*

- Cynthia has over 25 years of experience as a clinical educator in blood safety and the blood products fractionation industry.
- Cynthia's hospital career began at the University of Illinois in Chicago which included roles in hospital pharmacy management and clinical research in plasma and recombinant therapies, and participation on multiple hospital committees related to the provision of blood products and patient safety.
- In her current role, Cynthia is focused on educating clinicians in transfusion medicine and blood banking, and other disciplines who utilize blood products for their patients on the importance of blood safety and pathogen reduction.



2

## Speaker Disclosure

- Cynthia is an employee and stockholder of Cerus Corporation. I have no other disclosures to report .



3

## Objectives

- Learn about the advancement of hemorrhage control and the MTP
- Discuss the importance of fibrinogen and what makes a healthy clot
- Assess early replacement of fibrinogen in bleeding patients
- Differentiate Cryoprecipitated AHF (Cryo AHF), Fibrinogen Concentrates, and Pathogen Reduced Cryoprecipitated Fibrinogen Complex
- Analyze studies focusing on fibrinogen replacement



4

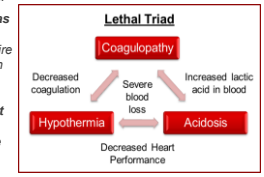
## Hemorrhage Control & Addressing Coagulopathy



5

## 1:1:1 Ratio and MTP History

- In 2007 Holcomb et al published the clinical experience treating combat casualties in Operation Iraqi Freedom and Operation Enduring Freedom in the Journal of Trauma.[1]
- Combat casualty treatment was utilizing a technique called "Damage Control Resuscitation" with improved outcomes.
- *"**Direct treatment of coagulopathy has been relatively neglected.**...Damage control resuscitation addresses the entire lethal triad immediately upon admission to a combat hospital. By demonstrating that in the severely injured **the coagulopathy of trauma is present at admission, recent studies have brought back to light the importance of treating this disorder at an earlier stage**"*[1]




**The massive transfusion protocol (MTP) reported in combat: 6 units of plasma, 6 units of PRBC, 6 packs of platelets and 10 units of cryoprecipitated AHF**

1. Holcomb JB, et al. J Trauma Acute Care Surg 2013;75:p S31-S39



6

## Earlier is Better in Hemorrhage Control

- In 2008, Cotton et al showed that faster, more aggressive resuscitation up front with blood products reduced mortality and overall blood component use [2]
- In 2017 Meyer et al (co-authored by Cotton), showed that every minute of delay between the activation of MTP, and the arrival of the first blood products, results in a 5% increase in the odds of mortality[3]
- Every effort should be made to decrease the time to administration of the first blood products


DELAY INCREASES MORTALITY[1]

2. Cotton BA, et al. Journ Trauma 2008;64:1177-83.
3. Meyer DE, et al. Journ Trauma 2017;83(1):p.19-24

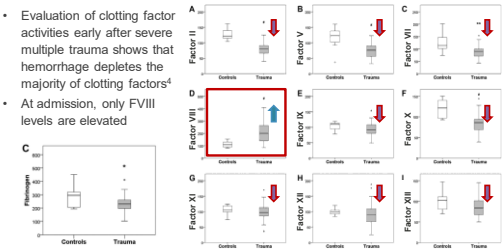


7

## Fibrinogen and Other Key Clotting Factors are Depleted during Trauma[4]

**Fibrinogen and Factors II, V, VII, IX, X, XI, XII and XIII are Depleted**

- Evaluation of clotting factor activities early after severe multiple trauma shows that hemorrhage depletes the majority of clotting factors[4]
- At admission, only FVIII levels are elevated







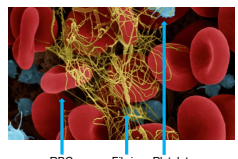
4. Burggraf M, et al. World J Emerg Surg 2015;10p:43

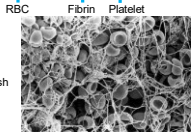


8

## Why Does Fibrinogen Matter?[5,6]

- At the site of injury, damaged tissue releases tissue factor and von Willebrand Factor (vWF) which recruit platelets and promotes thrombin generation
- These factors, and others from platelets, activate fibrinogen conversion to fibrin cross linking it to platelets and RBCs to make a clot
- Fibrinogen is key for clot formation (so that blood loss can be stopped)
- No fibrinogen, no clot



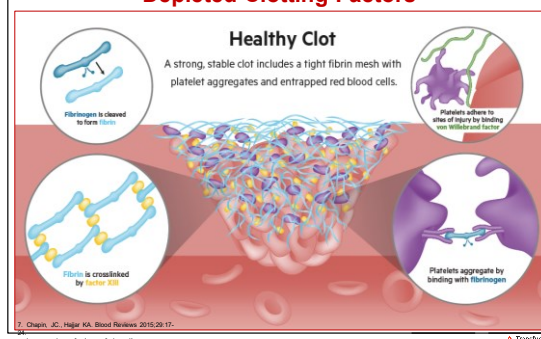

Credit: Electron micrograph of blood clot. David Gregory & Debbie Marshall. Attribution 4.0 International (CC BY 4.0)

5. Schoenecker J. Col SEM 2019.
6. Gregory, D., Marshall D. Attr. 4.0 (CC BY 4.0)



9

## Effective Treatment of Hemorrhage: Restore Depleted Clotting Factors[7]




7. Chapin, JC., Hajjar, KA. Blood Reviews 2015;29:17-24.



10

## Fibrinogen Level is an Independent Risk Factor for Hemorrhage

- Fibrinogen level decreases rapidly and significantly during hemorrhage[8,9]
- Levels in the low 200 mg/dL range is an independent risk factor for severe hemorrhage in[10,11]:
  - Trauma[10]
  - CV Surgery[11]
  - Obstetric Postpartum Hemorrhage[12]
- Studies have shown that early fibrinogen supplementation restores clot strength, reduces blood loss, and decreases mortality[8]

8. Rourke C. et al. Journ Haemo 2012;10:1342-51.
9. Hippala ST. et al. Anaesth Analg 1995;81:360-5.
10. Hagemo JS. et al. Crit Care 2014;18:R62.
11. Ranucci M. et al. Annals of Thor 2016;102:78-85.
12. Charbit B. et al. Journ Haemo 2007;5:266-73.



11

## Fibrinogen Replacement Therapies Indications for Use

| | Acquired | Congenital |
|---|---|---|
| Cryoprecipitated AHF[13] | ✓ | ✓ |
| Pathogen Reduced Cryoprecipitated Fibrinogen Complex [14] | ✓ | ✓ |
| Fibrinogen Concentrates[15,16] | | ✓ |

13. AABB Circ of Info; 2021.
14. INTERCEPT Pl. Cerus Corp; 2021.
15. RIASTAP Pl. CSL Behring LLC; 2020.
16. FIBRYGA Pl. Octapharma; 2020.



12

## Cryoprecipitated Antihemophilic Factor or Cryo AHF [13]

- Cryo AHF is an enriched source of fibrinogen and other key clotting factors that are depleted during hemorrhage
- These clotting factors include:
  - Fibrinogen
  - von Willebrand Factor (vWF)
  - Factor VIII
  - Factor XIII
  - Other vital clotting proteins

Cryo AHF Sample Label


13. AABB Circ of Info; 2021



13

## Cryo AHF Indications for Use[13]

- Used in the control of bleeding associated with fibrinogen deficiency, and when recombinant and/or virally inactivated preparations of fibrinogen, Factor VIII, Factor XIII, or vWF are not readily available.
- Second-line therapy for von Willebrand disease (vWD) and hemophilia A (Factor VIII deficiency).
- Replacement therapy in von Willebrand disease, Factor VIII or Factor XIII deficiency with active bleeding or undergoing an invasive procedure when commercial factor concentrate is not available
- Control of uremic bleeding after other modalities have failed

13. AABB Circ of Info; 2021



14

## Pathogen Reduced Cryoprecipitated Fibrinogen Complex[14]

- Pathogen Reduced Cryoprecipitated Fibrinogen Complex is an enriched source of fibrinogen and other key clotting factors that are depleted during hemorrhage
- These clotting factors include:
  - Fibrinogen
  - von Willebrand Factor (vWF)
  - Factor XIII
  - Other vital clotting proteins

Pathogen Reduced Cryoprecipitated Fibrinogen Complex Sample Label


14. INTERCEPT PI. Cerus Corp; 2021.



15

## Pathogen Reduced Cryoprecipitated Fibrinogen Complex[14]

- FDA recent approval with Breakthrough Device Status
- Cryoprecipitated from pathogen reduced (psoralen/UVA light) plasma
- Broad spectrum transfusion risk reduction due to inactivation of viruses, bacteria, and other pathogens
- ≤ 12 months frozen shelf life
- 5-days post-thaw shelf life


14. INTERCEPT PI. Cerus Corp; 2021.



16

## Pathogen Reduced Cryoprecipitated Fibrinogen Complex Indications for Use[14]

- Treatment and control of bleeding, including massive hemorrhage, associated with fibrinogen deficiency.
- Control of bleeding when recombinant and/or specific virally inactivated preparations of factor XIII or von Willebrand factor (vWF) are not available.
- Second-line therapy for von Willebrand disease (vWD)
- Control of uremic bleeding after other treatment modalities have failed.

*Limitations of Use*
Pathogen Reduced Cryoprecipitated Fibrinogen Complex should not be used for replacement of factor VIII

14. INTERCEPT PI. Cerus Corp; 2021.



17

## Fibrinogen Concentrates[15,16]

**RIASTAP®[15]**

- Lyophilized 900-1300 mg/vial
- Requires reconstitution prior to use
- Indicated for congenital hypofibrinogenemia

**fibryga®[16]**

- Lyophilized ~1g/vial
- Requires reconstitution prior to use
- Indicated for congenital hypofibrinogenemia


15. RIASTAP PI, CSL Behring LLC, July, 2020.
16. Fibryga PI Octapharma USA, Inc December, 2020.



18

## Fibrinogen Concentrates Indications for Use[15,16]

**RIASTAP®[15]**

**INDICATIONS AND USAGE**

RIASTAP®, Fibrinogen Concentrate (Human) is a human blood coagulation factor

- Indicated for the treatment of acute bleeding episodes in pediatric and adult patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia

**fibryga®[16]**

**INDICATIONS AND USAGE**

FIBRYGA is a human fibrinogen concentrate.

- Indicated for the treatment of acute bleeding episodes in adults and children with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia

FIBRYGA is not indicated for dysfibrinogenemia

15. RIASTAP PI, CSL Behring LLC; July, 2020.
16. Fibryga PI Octapharma USA, Inc; December, 2020.

19 | www.transfusionsafetyonline.com

19

## Limitations of Fibrinogen Sources

20 | www.transfusionsafetyonline.com

20

## Cryo AHF & Pathogen Reduced Cryoprecipitated Fibrinogen Complex

**Cryo AHF[13]**

- Thawing time
- 4-6-hour shelf life
- Not required to be prepared from pathogen reduced plasma

**Pathogen Reduced Cryoprecipitated Fibrinogen Complex[14]**

- Not indicated for the replacement of Factor VIII

13. AABB Circ of Info; 2021.
14. INTERCEPT PI, Cerus Corp; 2021.

21 | www.transfusionsafetyonline.com

21

## Cryo AHF Contraindications[13]

**CONTRAINDICATIONS**

- Do not use this component unless the results of laboratory studies indicate a specific hemostatic defect
- Cryo AHF should not be used if virus inactivated specific factor concentrates or recombinant factor preparations are available for management of patients with von Willebrand disease, hemophilia A or Factor XIII deficiency

13. AABB Circ of Info; 2021

22 | www.transfusionsafetyonline.com

22

## Pathogen Reduced Cryoprecipitated Fibrinogen Complex Contraindications, Warnings, Precautions[14]

**CONTRAINDICATIONS**

- Contraindicated for preparation of blood components intended for patients with a history of hypersensitivity reaction to amotosalen or other psoralens
- Contraindicated for preparation of blood components intended for neonatal patients treated with phototherapy devices that emit a peak energy wavelength less than 425 nm or have a lower bound of the emission bandwidth <375 nm, due to the potential for erythema resulting from interaction between ultraviolet light and amotosalen

**WARNINGS AND PRECAUTIONS**

- Only the INTERCEPT Blood System for Cryoprecipitation is approved for use to produce Pathogen Reduced Cryoprecipitated Fibrinogen Complex
- For management of patients with vWD or factor XIII deficiency, Pathogen Reduced Cryoprecipitated Fibrinogen Complex should not be used if recombinant or specific virally-inactivated factor preparations are available. In emergent situations, if recombinant or specific virally-inactivated factor preparations are not available, Pathogen Reduced Cryoprecipitated Fibrinogen Complex may be administered

14. INTERCEPT PI, Cerus Corp; 2021.

23 | www.transfusionsafetyonline.com

23

## Fibrinogen Concentrates

| RIASTAP[15] | FIBRYGA[16] |
|---|---|
| • Reconstitution time: Product must be fully dissolved before it is prepared for patient administration | • Reconstitution time: Product must be fully dissolved before it is prepared for patient administration |
| • Once reconstituted: stable for 8 hours at 20-25ºC | • Once reconstituted: stable for 4 hours at 20-25ºC |
| • No other clotting factors quantified in PI | • No other clotting factors quantified in PI |
| • RIASTAP is not indicated for dysfibrinogenemia | • Fibryga is not indicated for dysfibrinogenemia |

15. RIASTAP PI. CSL Behring LLC; 2020.
16. FIBRYGA PI. Octapharma, Inc; 2020.

24 | www.transfusionsafetyonline.com

24

## RIASTAP®
## Contraindications, Warnings and Precautions[15]

**CONTRAINDICATIONS**

RIASTAP is contraindicated in patients with known anaphylactic or severe systemic reactions to human plasma-derived products.

**WARNINGS AND PRECAUTIONS**

**Hypersensitivity Reactions** Allergic reactions may occur. If signs or symptoms of anaphylaxis or hypersensitivity reactions (including hives, generalized urticaria, tightness of the chest, wheezing, hypotension) occur, immediately discontinue administration The treatment required depends on the nature and severity of the reaction.

**Thrombosis** Thrombosis may occur spontaneously in patients with congenital fibrinogen deficiency with or without the use of fibrinogen replacement therapy. Thromboembolic events have been reported in patients treated with RIASTAP. Weigh the benefits of RIASTAP administration versus the risk of thrombosis. Monitor patients receiving RIASTAP for signs and symptoms of thrombosis.

**Transmissible Infectious Agents** Because RIASTAP is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-106 Jakob disease (CJD) agent. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by a process demonstrated to inactivate and/or remove certain viruses during manufacturing Despite these measures, such products may still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. All infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to CSL Behring Pharmacovigilance at 1-866-915-6958.

15. RIASTAP PI. CSL Behring LLC; 2020.



25

## FIBRYGA®
## Contraindications, Warnings and Precautions[15]

**CONTRAINDICATIONS**

FIBRYGA is contraindicated in individuals who have manifested severe immediate hypersensitivity reactions, including anaphylaxis, to FIBRYGA or its components (Sodium Citrate Dihydrate; Glycine; L-Arginine hydrochloride).

**WARNINGS AND PRECAUTIONS**

**Hypersensitivity Reactions** Hypersensitivity reactions may occur. If early signs of hypersensitivity reactions (including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis) or symptoms of allergic reactions occur, immediately discontinue administration. The treatment required depends on the nature and severity of the reaction.

**Thrombosis** Thrombosis may occur spontaneously in patients with congenital fibrinogen deficiency with or without the use of fibrinogen replacement therapy. Thrombotic events have been reported in patients receiving FIBRYGA. Treatment with human fibrinogen concentrate has been associated with risk of thrombosis at target fibrinogen levels that were less than 150 mg/dL. The risk of thrombosis may be greater when the target fibrinogen plasma level is 150 mg/dL.Weigh the benefits of FIBRYGA administration versus the risks of thrombosis. Patients receiving FIBRYGA should be monitored for signs and symptoms of thrombosis.

**Transmissible Infectious Agents** FIBRYGA is made from human plasma. Products made from human plasma may contain infectious agents (e.g., viruses and the CJD agent that can cause disease). Also, unknown infectious agents may be present in such products. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by a process demonstrated to inactivate and/or remove certain viruses during manufacturing. Despite these measures, such products may transmit disease. All infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Octapharma at 1-866-766-4860.

16. FIBRYGA PI. Octapharma, Inc; 2020



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## Why Does the Fibrinogen Source Matter?[17]

**Table 1.** Constituents of fibrinogen sources.

| | | | Cryo AHF | Fibrinogen Concentrate |
|---|---|---|---|---|
| | PNP | FDP | Cryoprecipitate | Fg-C |
| 1-5 Clauss Fg (g/L) | 3.3 ± 0.3 | <0.15 | 6.8 ± 0.1 | 21.6 ± 0.1 |
| 1-5 FII (%) | 98 ± 4 | 98 ± 7 | 101 ± 12 | <1 |
| 1-5 FV (%) | 82 | 36 ± 0.7 | 68 ± 9 | <1 |
| 1-5 FVII (%) | 84 ± 1 | 75 ± 4 | 81 ± 7 | <1 |
| 1-5 FVIII (%) | 107 ± 14 | 43 ± 5 | 190 ± 0.6 | <1 |
| 1-5 FIX (%) | 127 ± 25 | 106 ± 3 | 105 ± 8 | 2 |
| 1-5 FX (%) | 92 ± 7 | 95 ± 3 | 98 ± 14 | <1 |
| 1-5 FXI (%) | 100 ± 16 | 107 ± 4 | 92 ± 3 | <1 |
| 1-5 FXIII (%) | 80 ± 7 | <5 | 105 ± 3 | <1 |
| 1-5 vWF:Ag (%) | 127 ± 33 | 65 ± 1 | 288 ± 66 | 66 |
| 1-5 $\alpha_2$AP (μg/mL) | 72 ± 20 | 38 ± 3 | 98 ± 8 | 1 ± 3 |

Clauss fibrinogen and coagulation factors II, V, VII, VIII, IX, X, XI, XIII and vWF antigen were quantified using a Sysmex CS-5100 haematology analyser in pooled normal plasma (PNP), fibrinogen-deficient plasma (FDP), cryoprecipitate and fibrinogen concentrate (Fg-C). Results are represented by the mean ± SD and expressed as a percentage (%) of normal, except for Clauss fibrinogen which is reported as a concentration (g/L). The normal range for all factor assays is 50–150% and Clauss fibrinogen 1.5–4.5 g/L. $n = 2$. $\alpha_2$AP levels were quantified using an in-house enzyme-linked immunosorbent assay (ELISA). $n = 7$.

17. Morrow GB, et al. Int J Mol Sci 2021;22:2185



27

## Therapy for Traumatic Coagulopathy: Does the Fibrinogen Source Matter?[17]

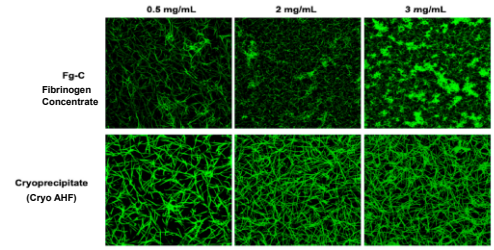


**Figure 5.** The fibrin network of thrombi formed from cryoprecipitate are more homogeneous than those formed from fibrinogen concentrate. Clots were formed from 30% PNP or FDP and spiked with 0.5, 2 or 3 mg/mL cryoprecipitate or fibrinogen concentrate (Fg-C). Clots were imaged using a ×63 1.4 oil immersion objective and Zeiss 710 laser scanning confocal microscope. Representative image of $n = 3$.

17. Morrow GB, et al. Int J Mol Sci 2021;22:2185



28

## Infectious Transmission Risk



29

## What is the Bacterial Risk Cryo AHF and Fibrinogen Concentrates

**Cryo AHF**

- Cryo AHF is limited to a 4-to-6-hour shelf-life post-thaw due in part to the risk of bacterial growth[18,19]
- Limited post-thaw shelf-life results in delayed access, due to need to thaw and potentially pool, and resistance to proactive thawing due to wastage risk[1,20]

**Fibrinogen Concentrates**

- Fibrinogen concentrates are made from human plasma
- Manufactured via a process demonstrated to inactivate and/or remove certain viruses[15,16]
- Transmission of unknown infectious agents is possible[15,16]

1. Holcomb JB, et al. J Trauma Acute Care Surg 2013;75:p.S31-S39
15. RIASTAP PI. CSL Behring LLC; 2020.
16. FIBRYGA PI. Octapharma; 2020.
18. Ramirez-Arcos S, et al. Vox Sang 2017;112(5):p.477-479.
19. Wagner SJ, et al. Transfusion 2019;59(11):p.3549-3550.
20. Holcomb JB, et al. J Trauma Acute Care Surg 2013;75:p.S31-S39.



30

## Bacteria Proliferates in Cryo AHF Stored at Room Temperature for >4 hrs[18]

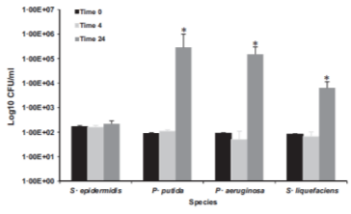


Fig. 1 Growth of bacteria in thawed cryoprecipitate stored at 20–24°C. Growth at 0 h (T0; black); 4 h (T4; light grey) and 24 h (T24; dark grey) for four bacteria is shown. Graphs show means ± SD for $n = 5$–10 with significant differences between T4 and T24 indicated by an asterisk.

**"While no strains grew in the first 4 hours, by 24 hours, three of four exhibited 1000-fold proliferation."**

18. Ramirez-Arcos S, et al. Vox Sang 2017;112(5):p.477-479.



31

## Bacterial Safety of Extended Room Temperature Storage of Thawed Cryoprecipitate (Cryo AHF) [19]

**"One of the limitations for use of cryoprecipitate (Cryo AHF) in this setting is that cryoprecipitate (Cryo AHF) must be transfused within 4 hours post thaw."**

TABLE 1. Bacterial contamination and time of first detection in cryoprecipitate

| Organism | Contamination source | Inoculum (CFU/unit) | Cryoprecipitate positive culture (Day 5 RT storage) | Time to first detection (hr) |
|---|---|---|---|---|
| *Staphylococcus epidermidis* PEI-B-P-06-01 | WB | 56, 37, 72 | 0 of 3 | NA |
| *Staphylococcus epidermidis* PEI-B-P-06-01 | Cryoprecipitate | 42, 37, 35 | 3 of 3 | 20.6, 32.3, 14.5 |
| *Klebsiella pneumoniae* PEI-B-P-08 | WB | 41, 39, 44 | 2 of 3 | 3.7, 3.8 |
| *Klebsiella pneumoniae* PEI-B-P-08 | Cryoprecipitate | 42, 54, 42 | 3 of 3 | 3.7, 3.8, 3.7 |
| *Staphylococcus aureus* PEI-B-P-63 | WB | 78, 73, 61 | 1 of 3 | 11.9 |
| *Staphylococcus aureus* PEI-B-P-63 | Cryoprecipitate | 94, 68, 68 | 3 of 3 | 6.0, 7.7, 5.2 |
| *Serratia marcescens* PEI-B-P-56 | WB | 61, 65, 56 | 2 of 3 | 3.7, 3.8 |
| *Serratia marcescens* PEI-B-P-56 | Cryoprecipitate | 54, 55, 50 | 3 of 3 | 3.8, 3.8, 3.8 |
| *Pseudomonas fluorescens* PEI-B-P-77 | WB | 59, 40, 48 | 3 of 3 | 3.8, 3.8, 4.0 |
| *Pseudomonas fluorescens* PEI-B-P-77 | Cryoprecipitate | 52, 42, 46 | 3 of 3 | 4.2, 3.8, 4.1 |
| *Escherichia coli* PEI-B-P-19 | WB | 37, 59, 57 | 0 of 3 | NA |
| *Escherichia coli* PEI-B-P-19 | Cryoprecipitate | 41, 45, 47 | 3 of 3 | 7.5, 4.3, 8.6 |
| *Streptococcus pyogenes* PEI-B-P-20 | WB | 41, 69, 81 | 1 of 3 | 8.8 |
| *Streptococcus pyogenes* PEI-B-P-20 | Cryoprecipitate | 37, 77, 68 | 3 of 3 | 7.3, 8.0, 8.2 |
| *Enterobacter cloacae* PEI-B-P-43 | WB | 42, 47, 49 | 0 of 3 | NA |
| *Enterobacter cloacae* PEI-B-P-43 | Cryoprecipitate | 57, 44, 44 | 3 of 3 | 3.7, 5.6, 13.2 |
| *Streptococcus dysgalactiae* PEI-B-P-71 | WB | 56, 56, 36 | 1 of 3 | 5.6 |
| *Streptococcus dysgalactiae* PEI-B-P-71 | Cryoprecipitate | 31, 51, 30 | 3 of 3 | 5.7, 7.7, 8.7 |

NA = not applicable; RT = room temperature; WB = whole blood.

19. Wagner SJ, et al. Transfusion 2019; 59(11):p.3549-3550.



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## Comparison of Bacterial Risk in Cryo AHF and Pathogen Reduced Cryoprecipitate Fibrinogen Complex[21]

**Table 3.** Assessment of high inoculum Staphylococcus epidermidis survival during and after the process of manufacturing PRCFC and cryo AHF for 5 days post-thaw storage.

| Manufacturing Step | | Titer (cfu/mL) | |
|---|---|---|---|
| | | Pathogen reduced Cryoprecipitate Fibrinogen Complex | Cryo AHF |
| Plasma Pre-Freeze | | $4.8 \times 10^6$ | $4.8 \times 10^6$ |
| Plasma Post-treatment | | UD [b] | - |
| Plasma Post-Thaw | | UD | Too numerous to count [a] |
| Second Pre-Freeze | | UD | Too numerous to count [a] |
| Second Post-Thaw | 0 h | UD | $1.6 \times 10^7$ |
| | 5 d | UD | $1.8 \times 10^7$ |

[a] Further dilutions were not assessed for titer calculation. [b] UD = undetectable.

- **Once Cryo AHF is thawed, the shelf life is 4-6 hours due in part for the potential of bacterial contamination**
- **Thawing Cryo AHF is typically on receipt of a patient specific order. The lack of proactive thawing of Cryo AHF may delay fibrinogen replacement**

21. Lu T, et al. Path 2022;11:744



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## The Importance of Fibrinogen in Hemorrhage Treatment:

### Growing Evidence that Earlier is Better



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## Trauma



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## The Ratio of Fibrinogen to Red Cells Transfused Affects Survival in Casualties Receiving Massive Transfusion[10]

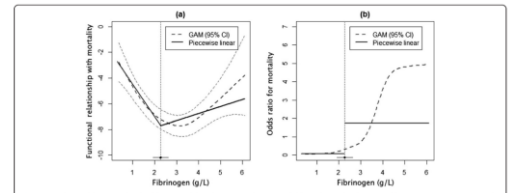



**Figure 1 Multivariable generalised additive model and piecewise linear model for relationship between fibrinogen concentration and 28-day survival.** Results from the multivariable generalised additive model (GAM) and the piecewise linear model for the relationship between fibrinogen concentration and 28-day survival, adjusted for Injury Severity Score, age, time from injury, mechanism of injury, base excess, International Normalized Ratio, platelet count and gender. The functional relationship is clearly nonlinear (**a**), resulting in a corresponding nonconstant odds ratio across the observed range of fibrinogen values (**b**). For the piecewise linear model, the breakpoint (95% confidence interval (CI)) is estimated at 2.29 (1.93, 2.64).

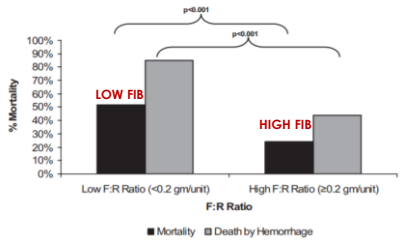
**"Trauma patients admitted less than 180 minutes post injury with fibrinogen levels below 229 mg/dL had a dramatic increase in mortality rate."**

10. Hagemo JS, et al. Crit Care 2014;18:R52.



36

## The Ratio of Fibrinogen to Red Cells Transfused Affects Survival in Casualties Receiving Massive Transfusion at an Army Combat Support Hospital[22]




**"An increased fibrinogen: RBC ratio was independently associated with improved survival."**

22. Stinger HK, et al. J Trauma 2008;64:p.S79-85.



37

## The Role of Cryoprecipitate (Cryo AHF) in Massively Transfused Patients: Results from the TQIP Database May Change Your Mind[23]

**"The use of cryoprecipitate (Cryo AHF) as an adjunct to massive transfusion in severely injured trauma patients may be associated with a marked reduction in mortality."**

| Table 2. Univariate Analysis of Outcomes | Cryo AHF | No Cryo AHF | |
|---|---|---|---|
| Variables | Cryoprecipitate (n=4,945) | No Cryoprecipitate (n=14,698) | *P-value* |
| 24-hrs Transfusion, units, median [IQR] | | | |
| pRBCs | 16 [10-27] | 20 [14-31] | <0.01 |
| Plasma | 11 [6-19] | 15 [10-23] | <0.01 |
| Platelets | 3 [2-5] | 3 [1-4] | 0.22 |
| Whole Blood | 1 [1-1] | 1 [1-1] | 0.77 |
| In-hospital complications, n (%)* | 1038 (50) | 3673 (49) | 0.36 |
| 24hrs mortality, n (%) | 1186 (24) | 4556 (31) | <0.01 |
| In-hospital mortality, n (%) | 2077 (42) | 7202 (49) | <0.01 |

IQR=Interquartile Range; pRBC=Packed Red Blood Cells; *=reported amongst those who survived their hospitalization

23. DiBlo M, et al. J Trauma Acute Care Surg 2020;89(2):p.336-343.



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## Early Cryoprecipitate (Cryo AHF) for Major Hemorrhage in Trauma: A Randomized Controlled Feasibility Trial[24]

**"The results of this study, raising possible associations between higher Fg (fibrinogen) blood concentrations, shorter ICU stay, and lower mortality, with no evidence of increased thrombotic events."**

Table 3 Clinical outcomes. Values are median (IQR) or n (%)

| | INTENTION TO TREAT | | | PER TREATMENT | | |
|---|---|---|---|---|---|---|
| | Cryo AHF | STANDARD | *P* value | Cryo AHF | STANDARD | *P* value |
| SUBJECTS | | | | | | |
| N | 20 | 21 | | 23 | 18 | |
| 28 day mortality | 2 (10.0) | 6 (28.6) | 0.14 | 3 (13.0) | 5 (27.8) | 0.22 |
| ICU Days | 11 (5–17) | 18 (16–20) | 0.56 | 13 (9–17) | 18 (13–23) | 0.81 |
| In patient Days | 31 (29–33) | 30 (22–38) | 0.66 | 32 (17–47) | 29 (21–37) | 0.08 |

24. Curry N, et al. J Anaesth 2015;115(1):p.76-83.



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## Association of Cryoprecipitate (Cryo AHF) and Tranexamic Acid with Improved Survival Following Wartime Injury: Findings from the MATTERs II Study[25]

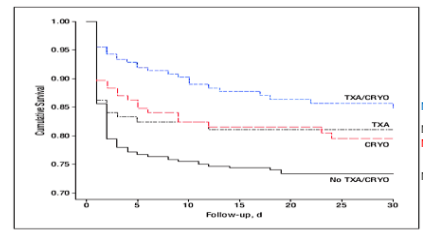


**Figure.** Survival plot of patients who received tranexamic acid and cryoprecipitate (TXA/CRYO), tranexamic acid alone (TXA), cryoprecipitate alone (CRYO), or neither product (no TXA/CRYO) as part of a component-based hemostatic resuscitation following combat injury.

**"Cryoprecipitate (Cryo AHF) may independently add to the survival benefit of tranexamic acid in the seriously injured requiring transfusion."**

25. Morrison JJ, et al. JAMA surg 2013;148:218-25.



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## Surgery



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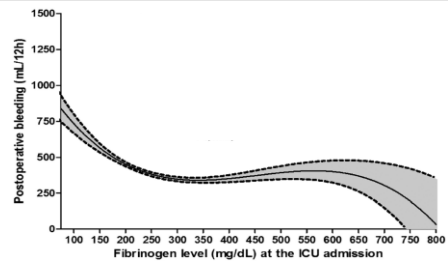
## Protocol Guided Bleeding Management Improves Cardiac Surgery Patient Outcomes[11]




**"In cardiac surgery, Fb levels lower than 220 mg/dL remained independently associated with severe bleeding, in active bleeding this raised to 375 mg/dL."**

11. Ranucci M, et al. Annals of Thor 2016;102:78-85.



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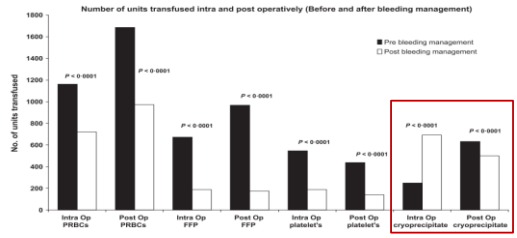
## Protocol Guided Bleeding Management Improves Cardiac Surgery Patient Outcomes[26]




**"Breakdown analysis of blood product use post protocol revealed a significant intra-operative decrease in the number of transfused units. Conversely for cryoprecipitate, the number of units transfused intra-operatively increased as did the percentage of patients receiving cryoprecipitate (Cryo AHF)."**

26. Pearse BL, et al. Vox Sang 2015;109(3):p.267-79.



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## Plasma Fibrinogen Level on Admission to the Intensive Care Unit is a Powerful Predictor of Postoperative Bleeding After Cardiac Surgery with Cardiopulmonary Bypass[27]

Table 4
Endpoints.

| Variable | Overall n = 1956 | Control group n = 1681 | Excessive bleeding group n = 189 | P |
|---|---|---|---|---|
| *Primary endpoint* | | | | |
| 24-h CTO (ml) | 728.6 ± 431.1 | 619.7 ± 238.4 | 1697.0 ± 539.7 | <0.0001 |
| *Secondary endpoints* | | | | |
| 6-h CTO (ml) | 332.5 ± 250.1 | 275.5 ± 144.4 | 836.4 ± 386.0 | <0.0001 |
| Fibrinogen level Day −1, (g/l) | 3.9 ± 1.1 | 4.0 ± 1.1 | 3.7 ± 1.2 | 0.031 |
| Fibrinogen level Day 0 (g/l) | 2.4 ± 0.8 | 2.5 ± 0.8 | 2.1 ± 0.8 | <0.0001 |
| Fibrinogen variation Day 0 (%) | −36.9 ± 17.8 | −36.2 ± 17.7 | −42.6 ± 17.7 | <0.0001 |
| Fibrinogen level Day 0 ≤ 2.2 g/l | 836 (45.3) | 710 (42.8) | 126 (67.0) | <0.0001 |
| Fibrinogen level Day 1 (g/l) | 3.4 ± 1.0 | 3.4 ± 1.0 | 2.9 ± 0.9 | <0.0001 |
| Fibrinogen variation Day 1 (%) | −10.6 ± 30.4 | −9.5 ± 29.8 | −18.2 ± 34.8 | 0.001 |
| Reoperation for bleeding | 73 (3.7) | 28 (1.7) | 39 (20.6) | <0.0001 |

The plus-minus values are the mean ± SD, and the others are no. (%). *P*-value, control group versus excessive bleeding group.
CTO, chest tube output; Day −1, preoperative; Day 0, admission in the intensive care unit; Day 1, First postoperative day; Fibrinogen variation, mean percentage variation of the fibrinogen level compared to the preoperative value.

**"At the time of admission to the intensive care unit, the fibrinogen level was significantly lower in the excessive bleeding group than in the control group."**

27. Kindo M, et al. Thromb Res 2014;134(2):p.360-8.



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# Obstetrics



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## The Decrease of Fibrinogen is an Early Predictor of the Severity of Postpartum Hemorrhage[12]

**"Our results further show that, once postpartum hemorrhage is diagnosed, the decrease in fibrinogen level can be used as an indicator of its severity in the hours to come."**

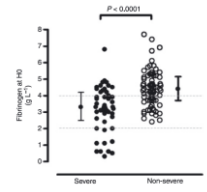


Fig. 2. Individual fibrinogen plasma concentrations at H0 in women with severe (●) or non-severe (○) postpartum hemorrhage. Mean ± SD values are reported for both groups.

Table 3 Multivariate logistic regression of laboratory parameters associated with severe PPH

| Time | Laboratory parameter | Number of patients | OR [95% CI] | *P*-value |
|---|---|---|---|---|
| H0* | fibrinogen (g $L^{-1}$) | 113 | 2.63 [1.66–4.16] | < 0.0001 |
| H1* | fibrinogen (g $L^{-1}$) | 114 | 2.70 [1.75–4.16] | < 0.0001 |
| H2† | fibrinogen (g $L^{-1}$) | 114 | 3.70 [2.17–6.25] | < 0.0001 |
| H4‡ | fibrinogen (g $L^{-1}$) | 115 | 5.00 [2.63–9.09] | < 0.0001 |

For fibrinogen, odds ratios (OR) were calculated for each 1 g $L^{-1}$ decrease in its plasma concentration. *data introduced in the model: INR, APTT, fibrinogen, factor II, factor V, D-dimer, antithrombin, protein C and TAT. †data introduced in the model: INR, APTT, fibrinogen, factor II, factor V, D-dimer, antithrombin and protein C. ‡data introduced in the model: platelets, INR, APTT, fibrinogen, factor II, factor V, D-dimer and protein C.

12. Charbit B, et al. Journ Haemo 2007;5:266-73.



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## Early Cryoprecipitate (Cryo AHF) Transfusion Versus Standard Care in Severe Postpartum Hemorrhage (PPH): A Pilot Cluster-Randomized Trial[28]

Table 3 Medical and surgical management for intervention (early cryoprecipitate (cryo)) and control (standard care) in women with postpartum haemorrhage (PPH). Values are mean (SD) or number (proportion).

| | Intervention n = 110 | Control n = 70 | Total n = 180 | Mean difference/ OR (95% CI)* |
|---|---|---|---|---|
| Estimated blood loss, ml | 2326 (985) | 2688 (1315) | 2467 (1135) | −362 (−701 to −23) |
| Initial blood values (first values during PPH) | | | | |
| Haemoglobin; $g.l^{-1}$ | 102 (17) | 97 (17) | 100 (17) | 5 (−0.6–10) |
| Platelets; $x10^9.l^{-1}$ | 174 (60) | 171.5 (60) | 173 (60) | 2.5 (−16–21) |
| Fibrinogen; $g.l^{-1}$, n = (37,41) [b] | 2.8 (1.3) | 3.1 (1.3) | 3 (1.3) | −0.3 (−0.9–0.3) |
| Blood transfusion requirements from PPH up to 24 h | | | | |
| RBC; units | 2.5 (1.8) | 3.1 (2.2) | 2.7 (2) | −0.6 (−1.2–0.0) |
| FFP; units | 0.8 (1.7) | 1.1 (1.6) | 0.9 (1.6) | −0.2 (−0.7–0.3) |
| Platelets; units | 0.1 (0.5) | 0.2 (0.6) | 0.2 (0.6) | −0.1 (−0.3–0.1) |
| Cryo; units[c] | 0.6 (1) | 0.7 (1.3) | 0.7 (1.1) | 0 (−0.4–0.3) |
| Total; units[c] | 4.1 (4) | 5.1 (5.2) | 4.5 (4.5) | −1 (−2.3–0.4) |
| Cell salvage (ml) up to 24 h, n = (5,2) | 317 (458) | 100 (141) | 255 (393) | |
| Intravenous fluids (l) up to 24 h | 2.3 (1.2) | 2.5 (1.2) | 2.4 (1.2) | −0.2 (−0.6–0.2) |
| Blood transfusion requirements from PPH to discharge | | | | |
| RBC; units | 2.5 (1.9) | 3.2 (2.3) | 2.8 (2.1) | −0.7 (−1.3 to −0.1) |
| FFP; units | 0.8 (1.7) | 1.1 (1.6) | 0.9 (1.6) | −0.2 (−0.7–0.3) |
| Platelets; units | 0.1 (0.5) | 0.2 (0.6) | 0.2 (0.6) | −0.1 (−0.3–0.1) |
| Cryo; units[c] | 0.7 (1) | 0.7 (1.3) | 0.7 (1.1) | 0 (−0.3–0.3) |
| Total; units[c] | 4.2 (4.1) | 5.2 (5.2) | 4.6 (4.6) | −1 (−2.4–0.4) |

28. Green L, et al. Anaesth 2022;77(2):p.175–184.



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## Early Cryoprecipitate (Cryo AHF) Transfusion Versus Standard Care in Severe Postpartum Hemorrhage (PPH): A Pilot Cluster-Randomized Trial[28]

| | Intervention N=110 | Control N=70 | Total N=180 | Mean difference/OR (95% CI) |
|---|---|---|---|---|
| Surgical Procedures | 50 (46%) | 41 (59%) | 91 (51%) | 0.6 (0.3–1.1) |
| Hysterectomy | 2 (2%) | 3 (4%) | 5 (3%) | |
| Uterine balloon | 24 (22%) | 28 (40%) | 52 (29%) | |
| Laparotomy and primary repair | 8 (7%) | 3 (4%) | 11 (6%) | |
| Other intra-abdominal packing | 7 (6%) | 10 (14%) | 17 (10%) | |
| Uterine artery embolisation | 2 (2%) | 0 | 2 (1%) | |
| Uterine tamponade | 0 | 4 (6%) | 4 (2%) | |
| Others[a] | 21 (19%) | 12 (17%) | 33 (19%) | |
| Mortality | 0 | 0 | 0 | |
| Admission to ICU | 6 (5%) | 9 (13%) | 15 (8%) | 0.4 (0.1–1.1) |

**"Cryoprecipitate (Cryo AHF) administration in severe PPH at any time-point was accompanied by reductions in RBC transfusions, surgery and ICU admission."**

28. Green L, et al. Anaesth 2022;77(2):p.175–184.



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## Fibrinogen Concentrate and Maternal Outcomes in Severe Postpartum Hemorrhage[29]

A Population-Based Cohort Study with a Propensity Score-Matched Analysis

Association between fibrinogen concentrate administration and its timing and maternal near-miss or death with multivariable and propensity score-matched analyses. Values are row proportion.

| | | | Maternal near-miss or death | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Multivariable analysis[a] | | | Propensity score analysis[b] | | |
| | | % of maternal near-miss or death | crude RR | [95% CI] | P | adjusted RR | [95% CI] | P | RR | [95% CI] | P |
| Fibrinogen concentrate administration | Yes | 24.6 | 1.58 | [1.17-2.13] | 0.003 | 1.03 | [0.73-1.49] | 0.855 | 0.85 | [0.55-1.32] | 0.477 |
| | No | 15.6 | 1 | | | 1 | | | 1 | | |

Among women who received fibrinogen concentrate (N = 313)

**"The use of fibrinogen concentrate in severe postpartum hemorrhage needing red cell transfusion during active bleeding is not associated with improved maternal outcomes."**

29. Delau F, et al. J of Clin Anesth 2022;81:110874.



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## Pediatrics



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## Association of Cryoprecipitate (Cryo AHF) Use With Survival After Major Trauma in Children Receiving Massive Transfusion[30]

Table 2. Propensity Score-Weighted 24-Hour Mortality Risk for Children Who Received Cryoprecipitate vs No Cryoprecipitate Within First 4 Hours of Arrival, Overall and by Subgroup

| Variable | No. | Cryoprecipitate, No. (%) | | Absolute risk difference, % (95% CI) | Relative risk (95% CI) |
|---|---|---|---|---|---|
| | | Yes | No | | |
| Unadjusted sample | 1948 | 128 (21.7) | 313 (22.3) | 1.4 (-2.8 to 5.6) | 1.1 (0.9 to 1.3) |
| Adjusted samples | | | | | |
| Overall | 1948 | 173 (18.0) | 245 (24.9) | -6.9 (-10.6 to -3.2) | 0.7 (0.6 to 0.9) |
| Age, y | | | | | |
| ≤10[a] | 563 | 31 (11.4) | 58 (20.0) | -8.5 (-14.9 to -2.2) | 0.6 (0.3 to 0.9) |
| >10 | 1380 | 144 (21.1) | 189 (27.2) | -6.1 (-10.7 to -1.5) | 0.8 (0.6 to 0.9) |
| Injury type | | | | | |
| Penetrating | 739 | 57 (15.6) | 93 (24.6) | -9.0 (-14.8 to -3.3) | 0.6 (0.5 to 0.9) |
| Blunt[a] | 1127 | 119 (21.1) | 147 (26.1) | -5.0 (-10.1 to 0.2)[b] | 0.8 (0.6 to 1.0) |
| Total blood transfused, 4 h, mL/kg[c] | | | | | |
| ≥100 | 600 | 94 (31.1) | 120 (40.2) | -9.0 (-16.0 to -2.0) | 0.8 (0.6 to 0.9) |
| <100[a] | 1346 | 67 (10.0) | 120 (17.7) | -7.7 (-11.7 to -3.7) | 0.6 (0.4 to 0.8) |
| Pediatric trauma center | | | | | |
| Yes | 1041 | 79 (15.2) | 114 (21.9) | -6.6 (-11.6 to -1.7) | 0.7 (0.5 to 0.9) |
| No[a] | 904 | 99 (22.2) | 130 (28.4) | -6.2 (-12.3 to 0.0)[b] | 0.8 (0.6 to 1.0) |

[a] To meet the overlap assumption, patients with propensity scores smaller than the default tolerance of $1.00 \times e^{-5}$ were excluded from the model.
[b] Blunt ($P = .059$); nonpediatric trauma center ($P = .049$).
[c] Total blood products transfused by 4 hours since triage.

**"Patients who received early cryoprecipitate (Cryo AHF) had a significantly lower 24- hour mortality rate when compared with those who did not."**

30. Tarna MA, et al. JAMA Surg 2021.



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## Summary

- Fibrinogen rapidly depletes in bleeding patients and is an independent indicator for severe hemorrhage
- Early fibrinogen replacement in bleeding patients may improve patient outcomes
- Cryo AHF and Pathogen Reduced Cryoprecipitated Fibrinogen Complex contain fibrinogen and additional clotting factors to treat bleeding patients
- Cryo AHF has a short shelf life of 4-to-6 hours due in part to bacterial risk
- Fibrinogen concentrates only include fibrinogen, require reconstitution and have a short 4-to-8-hour shelf life
- Pathogen Reduced Cryoprecipitated Fibrinogen Complex has a 5-day room temperature shelf life post-thaw, allowing for immediate use.



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## Questions?

[thank you]

Any questions? Please ask!!!

Cynthia Robbins
crobbins@cerus.com



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