Cryoprecipitated AHF: Challenges & Solutions

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Faculty Disclosure

No conflict of interest.
Objectives

• Review the challenges associated with manufacturing Cryoprecipitated AHF (Cryo)
• Impact of COVID-19 related disruptions to collections & manufacturing
• Potential of using PF24 as the source material to manufacture Cryo.
Challenges

• Source material is FFP, a timed product.
  – Only blood drives that are close to manufacturing site
• 1st stage Cryo collections require upfront planning: 3-bag kit, rather than 2-bag kit.
• Requirement of pooling by same blood type
• Manual process
• Manufacturing resource capacity
• Increasing demand – ~7% annualized.
COVID-19 impact

- Disruption to collections
- Manufacturing disruptions
- Competing priorities
- Staffing issues
- Lack of adequate supply of source material (FFP)
Solutions

- Donors – national appeals
- Manufacturing – additional manufacturing sites
- Staffing – ongoing hiring and training
- Source material – PF24 v/s FFP.
  (Most of the plasma collected by ARC is PF24).
Source material for Cryo

- Cryo AHF is manufactured from FFP frozen <8 hours in the US.
- AABB standards and US FDA CFRs mandate the use of FFP as source material.
- Cryo AHF shall contain $\geq 80$ IU/unit of FVIII and $\geq 150$ mg of fibrinogen/unit.
- FVIII is a labile protein and more variable in PF24.
Literature review

BLOOD COMPONENTS

Cryoprecipitate prepared from plasma frozen within 24 hours after phlebotomy contains acceptable levels of fibrinogen and VIIIC

Mark H. Yazer, Darrell J. Triulzi, Andrea Cortese Hassett, and Joseph E. Kiss

Yazer et al, 2010. Transfusion
### TABLE 1. Summary of clotting factor levels in cryo24 and standard cryo

<table>
<thead>
<tr>
<th>Clotting factor</th>
<th>Cryo24 (n = 20)</th>
<th>Standard cryo (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen (mg/unit)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>575.8</td>
<td>455.8</td>
</tr>
<tr>
<td>SD</td>
<td>185.9</td>
<td>172.6</td>
</tr>
<tr>
<td>Median</td>
<td>580.0</td>
<td>438.5</td>
</tr>
<tr>
<td>Range</td>
<td>171-972</td>
<td>159-841</td>
</tr>
<tr>
<td>p Value</td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>VIII:C (IU/unit)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>252.4</td>
<td>216.1</td>
</tr>
<tr>
<td>SD</td>
<td>70.1</td>
<td>53.0</td>
</tr>
<tr>
<td>Median</td>
<td>232.5</td>
<td>217.0</td>
</tr>
<tr>
<td>Range</td>
<td>164-408</td>
<td>136-338</td>
</tr>
<tr>
<td>p Value</td>
<td></td>
<td>0.07</td>
</tr>
<tr>
<td>VWF:Ag (IU/unit)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>505.9</td>
<td>448.1</td>
</tr>
<tr>
<td>SD</td>
<td>135.1</td>
<td>118.9</td>
</tr>
<tr>
<td>Median</td>
<td>445.0</td>
<td>408.0</td>
</tr>
<tr>
<td>Range</td>
<td>340-828</td>
<td>279-666</td>
</tr>
<tr>
<td>p Value</td>
<td></td>
<td>0.16</td>
</tr>
</tbody>
</table>

Yazer et al, 2010. Transfusion
Plasma and cryoprecipitate manufactured from whole blood held overnight at room temperature meet quality standards

Katherine Serrano, Ken Scammell, Sandra Weiss, Brankica Culibrk, Elena Levin, Maria Gyöngyössy-Issa, and Dana V. Devine

Serrano et al, 2010. Transfusion
**TABLE 3. Coagulation factor validation measurements in cryoprecipitate**

<table>
<thead>
<tr>
<th>Production method</th>
<th>Fibrinogen (mg/unit)</th>
<th>FVIII (IU/unit)</th>
<th>FXIII activity (U/unit)</th>
<th>VWF (antigen level, U/unit)</th>
<th>VWF (ristocetin cofactor activity, IU/unit)</th>
<th>VWF (collagen-binding activity, U/unit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same-day WBF (n = 10)</td>
<td>308 ± 99</td>
<td>174 ± 56</td>
<td>38 ± 53</td>
<td>238 ± 59</td>
<td>130 ± 43</td>
<td>549 ± 163</td>
</tr>
<tr>
<td></td>
<td>(176-464)</td>
<td>(112-276)</td>
<td>(4-180)</td>
<td>(157-339)</td>
<td>(73-222)</td>
<td>(381-883)</td>
</tr>
<tr>
<td>Overnight WBF (n = 40)</td>
<td>368 ± 116</td>
<td>136 ± 48†</td>
<td>118 ± 66‡</td>
<td>264 ± 100</td>
<td>245 ± 86‡</td>
<td>538 ± 237</td>
</tr>
<tr>
<td></td>
<td>(218-669)</td>
<td>(65-267)</td>
<td>(15-263)</td>
<td>(115-541)</td>
<td>(87-429)</td>
<td>(181-1053)</td>
</tr>
</tbody>
</table>

* Data are reported as mean ± SD (range).
† p < 0.05, versus same-day WBF.
‡ p < 0.01, versus same-day WBF.

Serrano et al, 2010. Transfusion
Literature Review

- Cryo is no longer used for FVIII replacement.
- Unnecessary FVIII QC testing.
- Adds unnecessary cost to manufacturing.
- Risks of QC failures – assay variability; not clinically relevant.
- Remove FVIII QC requirement and potentially rename Cryo AHF as “cryofibrinogen” to reflect the modern use of this product.

Goldfinger et al, 2014. Transfusion
ARC Internal QC Data
ARC Internal QC Data

BHQ Monthly Fib Cryo Results (Across Facilities)

BHQ Monthly Fib Cryo Pooled Results (Across Facilities)

Rolling 12 month average denoted in yellow

LSL = 150
Using PF24 as source material -

• Two potential pathways:
  – Cryo fibrinogen concentrate (CFC)
    • Blood product manufactured from PF24 with only claims for fibrinogen (and not FVIII).
  – Cryo AHF from PF24 (Cryo AHF 24)
    • Same as Cryo AHF but with a variance – using PF24 as source material rather than FFP.
CFC v/s Cryo AHF 24

CFC

- **Pros:**
  - Reflects current use of cryo
  - No need to test FVIII

- **Cons:**
  - New blood product
  - Updating SOPs
  - New product codes
  - Longer regulatory path

Cryo AHF 24

- **Pros:**
  - Same product
  - Faster regulatory path

- **Cons:**
  - Continue to test for FVIII
  - Potential for QC failures

Let data drive the strategy!
Cryo AHF 24: Feasibility Study

- Small feasibility study at one manufacturing site
- N=21 cryo singles from PF24 as source

Three worst-case scenario stacked for feasibility assessment:

- Type O
  (Type O donors are known to have lower FVIII levels compared to other blood types)
- Singles
  (Singles have more variability and thus higher likelihood of QC failure compared to pools)
- Frozen slightly less than 24 hours (20 to 24 hours)
  (Average time-to-freeze for PF24 is 17 hours at ARC)
Type O has lower FVIII than Type A

Feasibility Study Data

Thanks to Jenni White and Portland manufacturing team!
ARC Transfusion Innovation Lab

- Cryo from 6 FFP units and 6 PF24 units was compared.
- Levels of FVIII and fibrinogen in thawed Cryo were similar regardless of source material.
- Additional data to support Cryo AHF 24 strategy

Thanks to Dr. Bethany Brown and team!
### ARC Transfusion Innovation Lab

<table>
<thead>
<tr>
<th>Source</th>
<th>Blood type</th>
<th>Volume</th>
<th>FVIII</th>
<th>Fibr</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFP; 1-0</td>
<td>O-POS; Male</td>
<td>25</td>
<td>208</td>
<td>352</td>
</tr>
<tr>
<td>FFP; 2-0</td>
<td>O-POS; Male</td>
<td>25</td>
<td>174</td>
<td>520</td>
</tr>
<tr>
<td>FFP; 3-0</td>
<td>O-POS; Female</td>
<td>22</td>
<td>201</td>
<td>644</td>
</tr>
<tr>
<td>FFP; 1-A</td>
<td>A-POS; Male</td>
<td>20</td>
<td>309</td>
<td>515</td>
</tr>
<tr>
<td>FFP; 2-A</td>
<td>A-POS; Male</td>
<td>25</td>
<td>286</td>
<td>552</td>
</tr>
<tr>
<td>FFP; 3-A</td>
<td>A-POS; Female</td>
<td>20</td>
<td>247</td>
<td>509</td>
</tr>
<tr>
<td>PF24; 1-0</td>
<td>O-POS; Male</td>
<td>25</td>
<td>244</td>
<td>307</td>
</tr>
<tr>
<td>PF24; 2-0</td>
<td>O-NEG; Female</td>
<td>24</td>
<td>268</td>
<td>1008</td>
</tr>
<tr>
<td>PF24; 3-0</td>
<td>O-POS; Male</td>
<td>25</td>
<td>213</td>
<td>425</td>
</tr>
<tr>
<td>PF24; 1-A</td>
<td>A-POS; Male</td>
<td>22</td>
<td>238</td>
<td>485</td>
</tr>
<tr>
<td>PF24; 2-A</td>
<td>A-POS; Female</td>
<td>23</td>
<td>265</td>
<td>700</td>
</tr>
<tr>
<td>PF24; 3-A</td>
<td>A-POS; Male</td>
<td>15(^{(1)})</td>
<td>189</td>
<td>360</td>
</tr>
</tbody>
</table>

FVIII: 238 ± 53 IU
Fib: 515 ± 94 mg

FVIII: 236 ± 31 IU
Fib: 548 ± 264 mg

(1) Unit broken in transit.

Thanks to Dr. Bethany Brown and team!
The Red Cross designed and conducted a process control/validation study to demonstrate with a 95% confidence level that 95% of the Cryo products manufactured with WB PF24 would meet FVIII and fibrinogen acceptability criteria.

A minimum of twenty consecutive PF24 units from three (3) separate manufacturing sites (N ≥ 60) were manufactured into Cryoprecipitated AFH.

Final N = 69.
Process Control / Validation Results

Thanks to the manufacturing teams at St. Paul, MN; Pomona, CA and Johnstown, PA
FDA submission

• ARC is in the process of submitting data to the FDA to request a variance to allow use of PF24 (instead of FFP) as source material to manufacture single and pooled Cryo AHF.
• Other blood centers are also working towards this goal.
Interim suggestions

• Order pooled Cryo without ABO restrictions. (Hadjesfandiari, et al 2020).
• Consider keeping fibrinogen concentrate on the formulary.
• Prospective audits of Cryo orders.
• The amount of fibrinogen in pooled Cryo is significantly more than historically known.
• Consider using one pooled Cryo as an adult dose in non-bleeding patients.
BRIEF REPORT

Risk analysis of transfusion of cryoprecipitate without consideration of ABO group

Narges Hadjesfandiari$^{1,2}$ | Elena Levin$^{2,3}$ | Katherine Serrano$^{1,2,3}$ | Qi-Long Yi$^4$ | Dana V. Devine$^{1,2,3}$
Interim suggestions

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• Consider keeping fibrinogen concentrate on the formulary.
• Prospective audits of Cryo orders.
• The amount of fibrinogen in pooled Cryo is significantly more than historically known.
• Consider using one pooled Cryo as an adult dose in non-bleeding patients.
Summary

• Cryo production is susceptible to numerous challenges – Collections, Manufacturing, Staffing, Source material

• Producing Cryo AHF from PF24 is a potentially viable strategy to permanently solve one of those challenges.
Acknowledgements

Cryo AHF Core Team at ARC:

- Dr. Bethany Brown (Transfusion Innovation)
- Dr. Pampee Young (CMO)
- Steve Kassapian & Scott Webber (Regulatory Affairs)
- Jennifer White (Manager, supply chain)
- Leo Debandi (Production & Inventory)
- Manufacturing team
- Sales team
- Supply chain operations team
- Tim Washburn
Questions

Please post your question in the chat.

Alternatively, feel free to email me at parvez.lokhandwala@redcross.org

Thank you!