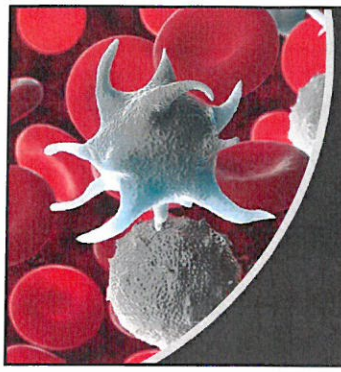

Bacterial Risk Control Strategies for Platelets

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System Medical Director Transfusion Service
Saint Luke's Health System

HAABB Virtual Meeting
December 2, 2020

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Disclosures

- None

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Agenda

- History of Platelet Transfusion
- Bacterial Contamination in Platelets
- Bacterial Risk Control Strategies and FDA's Final Guidance

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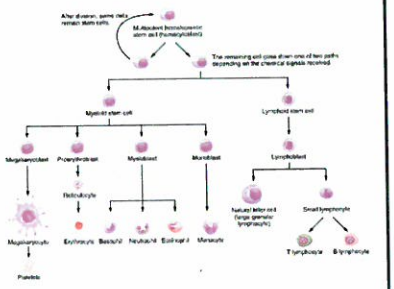
Platelets

- Circulating anucleate disc-shaped blood cell responsible hemostasis.



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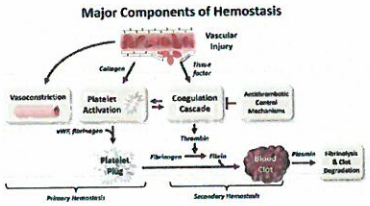
Discovery

- 1882 Italian pathologist Giulio Bizzozero discovered Platelets under microscope and described hemostatic function.



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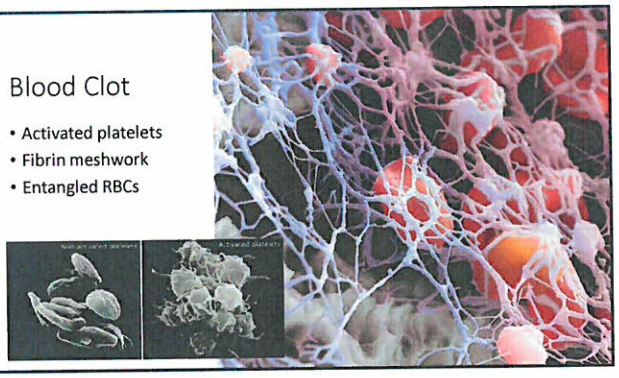
Blood Clot

- Activated platelets
- Fibrin meshwork
- Entangled RBCs



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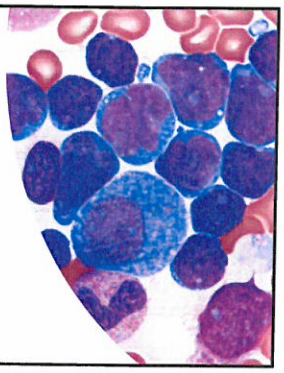
Origins of Platelet Transfusion Therapy



- Acute Lymphoblastic Leukemia (ALL) in children was 100% fatal illness with a median survival of 2 to 3 months.
- 1955 Dr. Emil J Freireich noticed chemotherapy used to often failed because of severe and often fatal hemorrhage.
- Bleeding was due to severe thrombocytopenia because of bone marrow suppression by chemotherapy.

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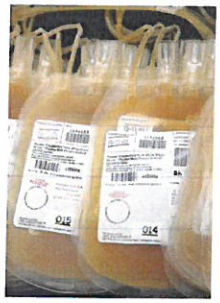
Origins of Platelet Transfusion Therapy



- Addition of fresh platelets in-vitro corrected all coagulation abnormalities.
- Role of Platelet transfusion therapy was identified and evaluated.
- Still, the road ahead was not easy!

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Road Block #1

- Stored donor whole blood could not be used.
- Steel needles, uncoated rubber tubing, and glass bottles used for blood collection severely depleted platelets.

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Plastic Bags

- 1950 plastic collection bags introduced.
- Functional platelets recovered when blood collected with siliconized needles and plastic bags (non-wettable surfaces).

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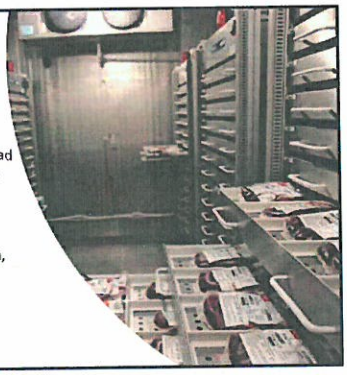
Road Block #2

- Platelets isolate from the blood that had been stored for more than 48 hours in cold conditions (4°C) had deleterious effect on life-span and function.
- To address the hemorrhage in children, freshly collected platelets have to be used.



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Room Temp Storage

- 1961 Platelet concentrates recognized to reduce mortality from hemorrhage in cancer patients.
- 1969 S. Murphy and F. Gardner demonstrate the feasibility of storing Platelets at room temperature (20-24C) for up to 3 days, revolutionizing platelet transfusion therapy.

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Platelet Transfusion Therapy

- For over 50 years platelet transfusions have been universally used to prevent and treat hemorrhagic diathesis due to thrombocytopenia.
  - Cancer patients
    - Hematologic (leukemia, myelodysplasia, aplastic anemia, etc.)
    - Solid tumors
    - Chemotherapy & bone marrow transplant support
  - Bleeding patients (Surgeries and trauma)
  - Congenital or acquired/medication-induced platelet dysfunction
  - Extracorporeal membrane oxygenation or cardiopulmonary bypass
  - And more....

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Road Block #3

- Reports of bacterial contamination & sepsis.
- Room temp stored platelets ideal culture media for bacteria.
- Risk of bacterial contamination of platelets approximately 1:1000-2000 unit.

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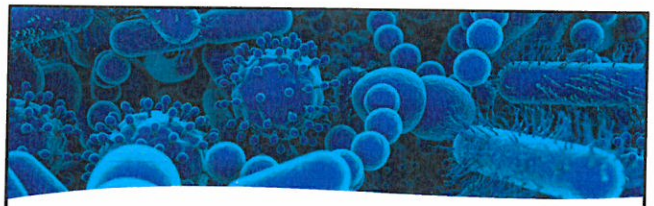

Bacterial Contamination Sources

- Contamination during whole blood collection (skin flora).
- Contamination of the collection pack (Leaky seals, damaged tubing, or micro-punctures in collection).
- Donor bacteremia.

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Bacterial Contaminants

Gram Positive

- Bacillus species
- Streptococcus species
- Staphylococcus species
- Propionibacterium acnes

Gram Negative

- *Klebsiella species*
- *Serratia species*
- *Escherichia coli*
- *Acinetobacter species*
- *Enterobacter species*
- *Providencia rettgeri*
- *Yersinia enterocolitica*

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Early Efforts to Reduce Bacterial Contamination

- During donation
  - Improved donor screening
  - Improved venipuncture site disinfection
- Optimizing blood component processing & storage
  - Optimize storage temperature
  - Limit storage time (5-day shelf-life)
- Pretransfusion bacterial detection
  - Visual inspection of components before issue
- Reduce recipient exposure to blood donors
  - Optimize transfusion indications & triggers (Blood utilization)
  - Increase use of apheresis-derived products

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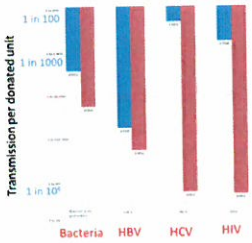
Any Progress?

- Bacterial contamination and associated fatalities still persisted.
- Leading cause of transfusion related fatalities reported to the FDA 1990-98, ~25-30/yr.



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Call For Immediate Action

- 2002 FDA Workshop in Bethesda, MD
- Direct bacterial culture required by FDA
- AABB standard 5.1.5.1 for (Approved 2003, Implemented 3/1/2004)
  - "The blood bank or transfusion service shall have methods to limit & detect bacterial contamination in all platelet components"
- Diversion pouches, removal of first aliquot of donor blood also adopted as standard practice.

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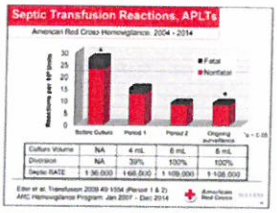
Outcome



- Culture and diversion pouch significantly decreased Septic reactions and fatalities

Period 1: March 1, 2004, to May 31, 2006
Period 2: December 1, 2006, and July 31, 2008

Eder, Anne F., et al. "Limiting and detecting bacterial contamination of apheresis platelets: inlet-line diversion and increased culture volume improve component safety." Transfusion 49.8 (2009): 1554-1563.

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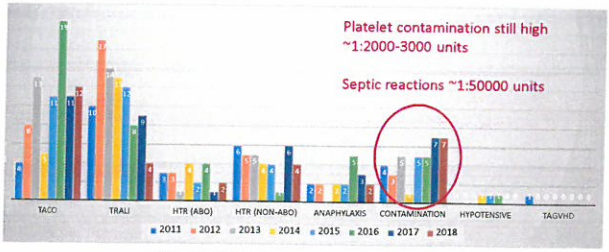
Where do we stand?



US Food and Drug Administration. "Fatalities reported to FDA following blood collection and transfusion, annual summary for fiscal year 2018".

21

Job Half Done!

- FDA: "Room temperature stored platelets are associated with a higher risk of sepsis and related fatality than any other transfusable blood component."
- Continued efforts needed to decrease platelet bacterial contamination, sepsis and fatalities.


Egg drop soup platelets: gross bacterial contamination of a platelet product

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New FDA Guidelines!

- "Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion"

Guidance for Industry
Released Sep 30, 2019
Effective Mar 30, 2021

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FDA Guidelines

- Guidance for blood centers and transfusion services
- Additional steps required to improve safety of platelet products
- Applies to apheresis and WB platelets
- 18-month implementation – Effective March 31, 2021

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Options to enhance Safety of Platelets

1. Primary culture + Secondary culture
2. Primary culture + Rapid bacterial testing
3. Large volume delayed sampling at 36 hrs/48 hrs
4. Pathogen reduction

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Current Practice- Primary Bacterial Culture

- Collect platelets
- Hold for at least 24 hrs
- Culture 8ml aerobic media only, culture on mother bag
- Incubated for at least 12 hrs
- Platelets are quarantined until primary culture result is available (minimum 36 hours from collection)
- 5 day shelf-life, ~ 3-4 day usable life

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Issues With Current Process

- Studies have shown that the sensitivity of the day 1 culture to detect contamination is <40%.
- Contaminated units may have a false negative culture due to sampling limitations with low initial numbers of bacteria.
- Units may be released and transfused before automated cultures turn positive.
- 5-100% of septic reactions and 100% of fatalities have occurred with transfusion of day 4 or 5 platelets.

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New Requirements

- Single-Step Strategies
- Two-Step Strategies

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New Requirements

- Single-Step Strategies
  1. Pathogen Reduction
  2. Large volume delayed sampling (LVDS) at 36 hours
  3. Large volume delayed sampling (LVDS) at 48 hours

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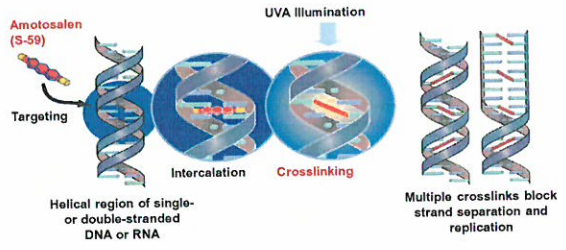
Pathogen Reduction



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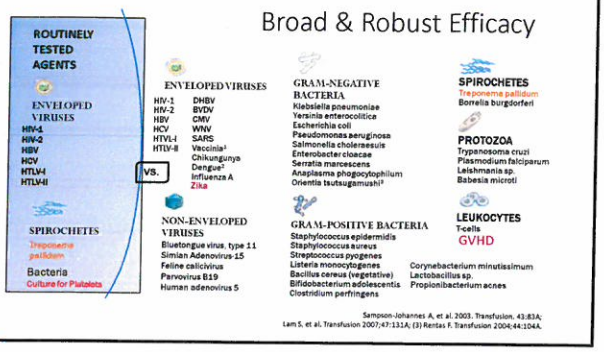
Broad & Robust Efficacy



Sampson-Johannes A, et al. 2003. Transfusion. 43:83A;
Lam S, et al. Transfusion 2007;47:131A; (3) Rentas F. Transfusion 2004;44:104A.

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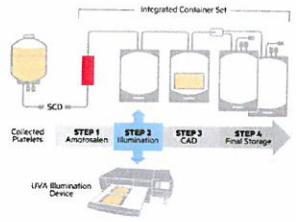
Process



- FDA-approved in 2014; in use in Europe for over a decade
- Good experience in European countries
- 5 day expiration

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Pathogen Reduction

Advantages

- No need to keep track of which units need testing
- No quarantine time, no false positives, no hands-on tech time for testing
- No need for CMV testing or irradiation, reduction
- Reduces risk of emerging transfusion-transmitted infection (eg. Zika)

Disadvantages

- Expensive, extra $100-150/unit
- At this time, no option for 7 day expiration
- Reduced increment, may require additional platelet transfusions
- Ongoing studies looking at incidence of associated respiratory reactions

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Large volume delayed sampling (LVDS)

- Large volume: 16ml total (aerobic, anaerobic media)
  - Culture on each split
- Delayed sampling: 36hr or 48hr
  - Hold 12h
- Shelf life: 5-day (36hr) & 7-day (48hr)

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LVDS

Advantages	Disadvantages
• Familiar method and equipment for blood centers	• Operationally challenging for blood centers
• No significant changes for transfusion service	• Excessive hands-on tech time
• Less costly option	• Increased positives due to anaerobic culture
• Option for 7 day expiration	• Reduced increment, may require additional platelet transfusions

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New Requirements

- Two-Step Strategies

  Step 1:
  1° culture at 24hr or LVDS at 36hr

  Step 2:
  1. 2° culture on ≥ Day 3
  2. 2° culture on ≥ Day 4
  3. 2° rapid bacterial testing

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Two-Step Strategies

Step 1

1. 1° culture at 24 hours, hold 12h
   - 16ml total (aerobic, anaerobic media)
   - Culture on mother bag
   - Usable up to Day 3

or

1. LVDS at 36 hours, hold 12h
   - Usable up to Day 5

plus one of the step 2

Step 2

1. 2° culture on ≥ Day 3, hold per SOP
   - 8ml total (aerobic medium)
   - 5-day expiration
2. 2° culture on ≥ Day 4, hold 12h
   - 16ml total (aerobic, anaerobic media)
   - 7-day expiration
3. 2° rapid testing on ≥ Day 3, transfuse within 24 hours
   - Transfuse within 24 hours
   - 5-7-day expiration

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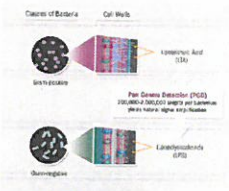
Rapid Bacterial Testing

- Detects conserved antigens in bacterial cell walls
  - Lipoteichoic acids on Gram positive bacteria
  - Lipopolysaccharides on Gram negative bacteria
- Used in conjunction with primary bacterial culture



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Rapid Bacterial Testing

Advantages

- Low cost, estimated cost $25-$35/test
- Rapid test time (~30 mins), easy to perform
- Small sample volume (500 µL)
- Allows for 7 day expiration, reduces expiration rates and associated costs
- Sensitive in detecting most bacteria, with low rate of false positives (<1%)

Disadvantages

- Performed at point of issue
- Logistic challenges to keep track of units to be tested each day and quarantine
- Relabeling requirements
- 36+ hr quarantine for 1° primary culture + short ~30 minute quarantine for rapid test
- False negatives require repeat testing and may result in some wastage

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FDA Guidelines Summary

Single-Step Strategies

Pathogen Reduction
- 5-day expiration

Large volume, delayed sampling (LVDS) at 36 hours, hold 12h
- 16ml total (aerobic, anaerobic media)
- Culture on each split
- 5-day expiration

Large volume, delayed sampling (LVDS) at 48 hours, hold 12h
- 16ml total (aerobic, anaerobic media)
- Culture on each split
- 7-day expiration

Two-Step Strategies

Step 1
- **Primary culture at 24 hours, hold 12h**
  - 16ml total (aerobic, anaerobic media)
  - Culture on mother bag
  - 5-day expiration (usable up to Day 3)

  or
- **LVDS at 36 hours, hold 12h**

Plus one of the following

Step 2
- **Secondary culture on ≥ Day 3**, hold per SOP
  - 8ml total (aerobic medium)
  - 5-day expiration
- **Secondary culture on ≥ Day 4**, hold 12h
  - 16ml total (aerobic, anaerobic media)
  - 7-day expiration
- **Secondary rapid testing**
  - Transfuse within 24 hours
  - 5 and 7-day expiration

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Shelf life 5 vs 7 days

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Summary

- Platelet bacterial contamination still a significant issue
- New FDA guidelines will be implemented by March 31, 2021
- Should improve safety of platelet transfusions
- Not sure about improved availability!

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Questions?

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