Options to Further Reduce the Risk of Bacterial Contamination in Platelets for Transfusion

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Outline

- Introduction
- Background on platelet storage and control of bacterial risk
- Recent FDA policy initiatives towards mitigating risk of bacterial contamination of platelets
- Current U.S. practices in bacterial testing
- Proposed considerations to further reduce the risk of bacterial contamination in apheresis platelets

Introduction

- Platelets are associated with a higher risk of sepsis and related fatality than any other transfusable blood component
  - Platelets are uniquely vulnerable to bacterial outgrowth due to their storage at room temperature (RT)
- Although reduced, this risk has persisted despite the interventions currently in place
- Currently platelets are stored at RT for a maximum of either 5 or 7 days depending on the preparation method, storage container, and bacterial risk control measures

Regulation on Controlling Bacterial Risk in Platelets

- Under 21 CFR 606.145 blood establishments and transfusion services are required to assure that the risk of bacterial contamination of platelets is adequately controlled. This requirement is currently met by:
  - Testing for bacterial contamination at least once

  or

  - Treating with an FDA-approved pathogen reduction device

5-day Platelet Storage

- Bacterial risk control is achieved
  - Most commonly by culture at least 24 hours after collection (primary testing)

  or

  - By treatment with an FDA-approved pathogen reduction device within 24 hours after collection

Extension to 7-day Storage

- For extension to 7 days, additional secondary testing (i.e. following the early primary culture) is permitted using a rapid test labeled as a 'safety measure'
  - 'Safety measure' indicates that testing of platelets proximate to transfusion has shown benefit for detection of contamination not revealed by previous primary bacterial testing
- Extension of dating beyond 5 days does not apply to pathogen-reduced platelets
  - Storage of apheresis platelets treated with FDA-approved pathogen reduction device is currently limited to 5 days

Recent FDA Policy Initiatives to Mitigate Risk of Bacterial Contamination in Platelets - I

- BPAC 2012: the Committee advised the use of secondary rapid testing on day 4 and day 5 transfusions to enhance safety of 5-day platelets

- December 2014: FDA published a draft Guidance document with considerations to enhance platelet safety and availability including BPAC's 2012 advice

Recent FDA Policy Initiatives in Mitigating Risk of Bacterial Contamination in Platelets - II

- March 2016: FDA published a revised draft Guidance document on controlling risk of bacterial contamination of platelets, with additional considerations:
  - Pathogen reduction, in lieu of early culture and secondary testing, to ensure safety of 5-day platelets
  - Extension to 7 days of suitably stored platelets that are secondarily tested with a test labeled as 'safety measure'
- May 2016: The Donor Eligibility Rule including 21 CFR 606.145 went into effect

Public Comments to FDA's 2016 Draft Guidance

- Will be summarized by FDA in the next presentation
- Introduced three proposed alternatives for primary and secondary bacterial testing
  - 5-day storage of apheresis platelets: Minimal Proportional Sampling Volume (MPSV) approach
  - 7-day storage of apheresis platelets
    - Large Volume and Delayed Sampling (LVDS) approach
    - Secondary bacterial culture testing on Day 4 following an early primary culture

Purpose of this Meeting

- FDA will ask the Committee whether specific alternative strategies for testing of platelets can provide adequate assurance of bacterial safety for both 5-day and 7-day apheresis platelets
- To inform the discussion, data will be presented on both apheresis and whole blood-derived platelets (WBDP)
  - Because the datasets for apheresis platelets are more extensive, and 7-day platelets in the U.S. are limited to apheresis platelets, questions for the Committee will focus only on apheresis platelets

Bacterial Testing of Apheresis Platelets

- Culture-based devices
  - Detection based on growth of bacterial organism (hours, days)
  - Analytical sensitivity (limit of detection) ~ 1 CFU/mL
  - Aerobic and anaerobic culture media
  - Can be used for primary or secondary testing
- Rapid tests
  - Non-culture based devices with direct detection of specific bacterial components
  - Analytical sensitivity: 10^3-10^5 CFU/mL depending on organism and testing device
  - Can be used for secondary testing

Traditional Practices for Bacterial Culture (Primary Testing) of Apheresis Platelets

- For over a decade apheresis platelets have been universally screened with a culture-based test
  - Sampling of main collection ≥ 24 hours after collection
  - 8 mL sampling volume inoculated into an aerobic culture medium
- Numerous studies on apheresis platelet products intended for transfusion have shown that the clinical sensitivity of the primary culture ranged only between 11% and 40% due to the limit of sampling at low bacterial load (sampling error)
- Bacterial residual risk exists on day of transfusion in spite of primary culture

Bacterial Detection and Sepsis Rates of 5-day Apheresis Platelets tested by Primary Culture

Primary Testing by Aerobic Culture 8 mL at ≥ 24 hours after collection	Bacterial Detection Rate on Day of Transfusion	Sepsis Rate
1/8,960 -1/3,965*	~1/2,400	-1/59,000 to 220,000 (per collection and by passive reporting) -1/10,000 (per component and by active reporting)

*Rates vary based on testing sites and apheresis collection platforms

Benefits of Addition of an Anaerobic Culture Medium

- Leads to increase in bacterial detection rate due to:
  - Sampling of additional volume from product
  - Growth of strict anaerobes that do not grow in an aerobic culture medium
- Faster growth of the facultative aerobes, with shorter detection time
- Rare fatal and non fatal septic reactions have been associated with anaerobes missed by the primary aerobic-only culture

Limitations of an Anaerobic Culture Medium

- Anaerobes rarely grow in the aerobic environment of a platelet product
- Primary culture testing using concurrent aerobic and anaerobic media showed that:
  - False positive (FP) rate of the anaerobic culture medium was 78.9% of reportedly positive collections
  - Of the confirmed contaminated products that were detected by the anaerobic-only culture medium:
    - ~ 60% were contaminated with low virulence, slow growing organisms (*Propionibacterium*, *Corynebacterium sp.*) that are detected late, often after the product has been transfused
    - ~35% were contaminated with species that were also identified in other collections in the same study and that grew in the aerobic medium, i.e. detection by the anaerobic culture medium likely related to increase in sampling volume rather than the medium itself *(E. coli, Staphylococcus, Streptococcus, Listeria, Gemella sp*.)
    - ~ 5%: *Haemophilus, Peptostreptococcus, Lactobacillus, Campylobacter sp.*

Practices for Rapid Testing of Apheresis Platelets

- Optimal sampling time ≥ 72 hours after collection
- Small sampling volume: 0.5-1mL, depending on testing device
- Read-out within 20 to 60 minutes
- Can be used in transfusion services within 24 hours of transfusion as a secondary test

Bacterial Detection and Sepsis Rates of 5-day Apheresis Platelets Tested by Secondary Rapid Test

- 27,620 apheresis units found negative by primary culture, underwent secondary rapid testing on Day of Transfusion (Days 2, 3, 4, or 5) within 24 hours of issuance[#]

Confirmed Detection Rate	False Positive Rate	False Negative Rate	Sepsis Rate
*9/27,620 = 1/3,069	142/27,620 = 0.51%	≥ 3/27,620 = ≥ 1/9,200	1/27,620 – 1/13,810 (active and passive reporting)

[#] Jacobs *et al*, Transfusion 2011:51:2573-2582

* Distribution of contaminated units by day of transfusion: four on Day 3, two on Day 4, three on Day 5

Minimal Proportional Sampling Volume (MPSV) for 5-day Platelets - I

- The predominant sampling practice for culture-based bacterial testing of platelets is to sample a *fixed* volume from the apheresis collection regardless of collection volume
- A new concept of minimal *proportional* sampling volume has been recently described:
  - The sampling volume is increased proportionally to apheresis collection volume to
    - Enhance the detection of bacterially contaminated platelets by decreasing sampling error
    - Ensure safety of 5-day platelets from bacterial contamination without secondary testing

Minimal Proportional Sampling Volume (MPSV) for 5-day Platelets - II

- Concept applied in a blood collection system in which apheresis platelets were collected during two study periods (And B) using the same apheresis collection platform
- Bacterial testing methodology was identical in the two periods except for the sampling volume
  - 8-10 mL in Period A (1.1%-2.7% of collection volume)
  - Minimal 3.8% proportional sampling volume in period B

Minimal Proportional Sampling Volume (MPSV) for 5-day Platelets - III

- Definitions for terms used in table on next slide following an initial positive instrument signal:
  - True positive: growth of same organism from culture bottle (CB) and platelet component (PC) and/or from patient
  - False positive: no growth from CB, and PC is negative or unavailable for confirmatory testing
  - Discordant negative: growth of organism from CB, but PC negative
  - Indeterminate: growth of organism from CB, but PC is unavailable for confirmatory testing

Minimal Proportional Sampling Volume for 5-day Platelets[#]	Period A -Sample time: 24-36 hours -Sampling volume: 8-10 mL (~1.8% of collection volume) -Aerobic bottle	Period B -Sample time: 24-36 hours -Sampling volume: ≥3.8% of collection volume -Aerobic bottle
Tested collections	188,389	159,098
True positive rate	$0.9/10^4$ collections	$1.83/10^4$ collections
False positive rate	$3.66/10^4$ collections	$15.05/10^4$ collections
Discordant negative rate	$3.13/10^4$ collections	$2.14/10^4$ collections
Indeterminate rate	$0.37/10^4$ collections	$0.63/10^4$ collections
Collections discarded and potentially harmful	$4.4/10^4$ collections (TP+DN+Indet)	$4.6/10^4$ collections (TP+DN+Indet)

[#] Kamel *et al*. Transfusion 2017;57;2413–2419

Minimal Proportional Sampling Volume for 5-day Platelets	Period A -Sample time: 24-36 hours -Sampling volume: 8-10 mL (~1.8% of collection volume) -Aerobic bottle	Period B -Sample time: 24-36 hours -Sampling volume: ≥3.8% of collection volume -Aerobic bottle
Tested collections	188,389	159,098
Collection associated with septic reactions (passive reporting)	1/188,389 (2 splits transfused to 2 patients)	1/159,098 (transfused to one patient)
Septic rate per component (split rate ~1.8%)	1/169,550 (passive reporting)	1/286,376 (passive reporting)

Minimal Proportional Sampling Volume for 5-day platelets

- Main advantages
  - Single culture conducted at the blood collection center
  - Doubled bacterial detection rate
  - Would obviate the need for secondary testing at the transfusion service

- Main drawbacks
  - Based on statements by the authors, MPSV requires upward adjustment of target settings for platelet collection to compensate for increased sample volume and to maintain apheresis collection split rates
  - ↑ FP rate, leading to discard of otherwise suitable products
  - Clinical benefit not yet demonstrated by comparison to the previous strategy at that institution

Bacterial Detection and Sepsis Rates of 5-Day Apheresis Platelets tested by Primary Culture

	Primary Testing By Aerobic Culture 8 mL at ≥ 24 hours after collection	MPSV Sampling 24-36 hours after Collection ≥ 3.8% sampling volume into Aerobic Culture Medium
Bacterial Detection Rate at Sampling Time	1/8,960 – 1/3,965*	1/5,464 ($1.83/10^4$)
Bacterial Detection on Day of Transfusion	~ 1/2,400	N/A
Sepsis Rate	- 1/59,000 to 220,000 (per collection and by passive reporting) - 1/10,000 (active reporting)	1/159,098 (per collection and by passive reporting)

* Rates vary based on testing sites and apheresis collection platforms

Large Volume (LV) and Delayed Sampling (DS) for 7-day Apheresis Platelets

- The extension of storage up to 7 days is based on a single culture using a Large Volume and Delayed Sampling strategy
- Large sampling volume = volume > traditional 8-10 mL sample
- Delayed sampling = sampling later than 24-36 hours after collection
  - Allows bacteria already present in the collection to proliferate further prior to sampling
- LV + DS = increase sensitivity for bacterial detection
- Strategy adopted by Héma-Québec in Canada, and by the National Health Service Blood and Transplant (NHSBT) in the U.K.

Implementation of LVDS for 7-day Stored Platelets at Héma-Québec

- In 2015, Héma-Québec implemented a Large Volume Delayed Sampling approach for testing apheresis and pooled platelets
- Large volume: 20 mL split evenly between aerobic and anaerobic culture media
- Delayed sampling: at least 48 hours after collection

Bacterial Detection and Sepsis Rates for Platelets at Héma-Québec Before and After LVDS[#]

	Sampling: Main Apheresis collection and Pools of WBDP	Bacterial Detection Rate at Sampling Time	Residual Bacterial Rate after Outdate	Septic Transfusion Reaction Rate (passive reporting)
2005-2014 **5 days**	8-10 mL (aerobic) at ≥ 24 hours	59/521,920 = **0.011%**	5/19,801 = **0.025%**	3/276,866 = **1/93,000** (fatalities: 1/276,866)
2015-2017 **7 days with LVDS**	20 mL (aerobic + anaerobic) at ≥ 48 hours	21/53,405 = **0.039%** (Apheresis platelets only: 14/44,190 = 0.032%)	**0/2804** (Apheresis platelets only: 0/2216)	**0/~80,000** (Apheresis platelets only: 0/66,000)

[#] Personal communication, Dr. Gilles Delage, Héma-Québec

Implementation of LVDS for 7-day Stored Platelets at NHSBT

- In 2011, NHSBT introduced screening of all platelet components for bacteria using a Large Volume Delayed Sampling approach
- Large Volume: 16 mL split evenly between aerobic and anaerobic culture media
  - ~ 7% volume of apheresis unit
- Delayed sampling: 36-48 hours after collection
- After a 6-hour incubation period, negative-to-date results qualify the products for 7-day storage

Bacterial Detection and Sepsis Rates for Platelets at NHSBT before and after LVDS#

	Platelet Product Type	True Positive Rate	False Positive Rate	Bacterial Detection Rate after Outdate	Septic Reaction Rate (passive reporting)	Risk of Contamination Proximate to Transfusion (False Negative Rate of LVDS)
2006-2010 **5 days**	Aph + WBDP pools	**No Upfront Bacterial Screening**		58 / 25,138 **~1/433**	10 / ~ 1,087,322 **~1/100,000**	10 + 5* / ~1,087,322 **~1/68,000**
2011-2015 **7 days with LVDS**	Aph + WBDP pools	403 / 1,239,029 **~1/3,075 (0.032%)**	2379 / 1,239,029 **~1/521 (0.19%)**	**0 / 4515**	**1 / 1,239,029**	1 + 3* / 1,239,020 **~1/312,500**

McDonald *et al*. Transfusion 2017;57:1122

* 5 and 3 apheresis units discarded upon visual inspection due to suspected and subsequently confirmed bacterial contamination

Bacterial Detection and Sepsis Rates for 7-day Apheresis Platelets at NHSBT with LVDS

	Platelet Product Type	True Positive Rate	False Positive Rate	Bacterial detection Rate after 7-day Outdate	Septic Reaction Rate (passive reporting)	False Negative Rate of Early Culture
2011-2015	Aph only	208 / 960,470 **= 1/4,618 (0.02%)**	2110 / 960,470 **=1/455 (0.22%)**	Not available	0 **~ 10^6**	3* / 960,470 **~ 1/320,000**

* 3 units discarded upon visual inspection due to suspected and subsequently confirmed bacterial contamination

Advantages of Large Volume Delayed Sampling

- Single bacterial test conducted at the blood collection center
- Increase in bacterial detection rate
- Enhanced availability of platelets with 7-day dating
- No reported septic reactions associated with transfusion of close to a million apheresis units, and one septic reaction after transfusion of ~ 1.25 million combined apheresis and pooled WBDP
- Would obviate need for secondary testing

Drawbacks of Large Volume Delayed Sampling

- With increased sampling volume, there is loss of therapeutic cellular product
- Increase of number of culture bottles to be processed
- Significant false positive rate leading to discard of otherwise suitable products
- Delay in sampling entails transfusion of older platelets

Rationale for 7-day Storage Based on Secondary Culture on Day 4

- Platelet transfusion-associated septic reactions and related fatalities rise on days 4 and 5 due to the proliferation of bacteria during storage
- A secondary culture on day 4 would be expected to identify contaminated units missed by the early culture

7-day Platelets at the Irish Blood Transfusion Service (IBTS) based on Day 4 Secondary Culture

- In 2005, IBTS implemented a strategy of re-culturing on Day 4, platelets that were negative by primary early culture and intended to be extended to 7 days
- Early culture
  - Sampling volume: 7.5 mL inoculated into each of an aerobic and anaerobic culture medium
  - Sampling time
    - Apheresis platelets: ≥ 13 hours after collection
    - WBD Pooled platelets: ≥ 30 hours after collection
- Day 4 culture: sampling volume identical to early culture

Bacterial Detection and Sepsis Rates for 7-Day Platelets at IBTS 2005-2016#

	Primary Culture TP Rate (Early Culture)	Day 4 Secondary Culture TP rate	Bacterial Detection Rate after 7-day Outdate	Septic Reaction Rate from 7-day platelets (passive reporting)
Aph + WBDP pools	87/171,956 **=0.05% (1/1,976)**	12/67,146 **=0.017% (1/5,600)**	0/2,800	0/~65,000
Aph only	29/106,337 **=0.027% (1/3,667)**	5/51,041* **=0.009% (1/10,214)**	0/2,169	0/~50,000

Personal communication, Dr. Stephen Field, IBTS

*Estimated number of donations retested on Day 4 based on a 2016 rate of 48%

Advantages and Drawback for 7-day Platelets with Day 4 Secondary Culture

- Advantages
  - Improved availability of platelets with extension to 7 days
  - Single secondary test that would obviate the potential need to repeat the secondary rapid test every 24 hours for 7-day extension
  - No reported septic transfusion reactions
- Drawback
  - In the U.S. the day 4 culture would be performed by the transfusion service unless platelet unit shipped back to a cooperating testing center

Bacterial Detection and Sepsis Rates of 7-day Platelets: Day 4 Culture vs. LVDS

		Early Primary Culture + Secondary Culture on Day 4 (IBTS) 8 mL into each Aer and Anaer	LVDS in Québec 48 hours 20 mL split into Aer and Anaer	LVDS in UK 36-48 hours 16 mL split into Aer + Anaer
Bacterial Detection Rate after 7-day Outdate	***Apheresis + WBDP pools***	0/2,800	0/2,804	0/4,515
	Apheresis platelets	0/2,169	0/2,216	Not available
Sepsis Rate	***Apheresis + WBDP pools***	0/~65,000	0/~80,000	*1/1,239,020
	Apheresis platelets	0/~50,000	0/~66,000	0/960,470

* One septic reaction following transfusion of a pooled WBDP

False Negative and Sepsis Rates Following Secondary Rapid Testing

- 27,620 apheresis units found negative by primary culture underwent secondary rapid testing on Day of Transfusion (Days 2, 3, 4, or 5) within 24 hours of issuance

Rapid Test False Negative Rate	Rapid Test False Negative Rate	Sepsis Rate (Active/Passive Reporting)	Sepsis Rate (Active/Passive Reporting)
On Day of Transfusion (Days 2, 3, 4, or 5) within 24 hours of Issuance	**Limited to Day 5 Transfusions within 24 hours of Issuance**	**Associated with Transfusion on Days 2, 3, 4, or 5**	**Limited to Day 5 Transfusions**
≥ 3/27,620 = ≥ 1/9,200	≥ 3/8,549 = ≥ 1/2850	1/27,620 – 1/13,810	1/8,549 – 1/4,274

Summary - I

- Bacterial contamination of platelets remains a public health concern
- FDA's March 2016 draft guidance document proposed use of:
  - Secondary testing to improve 5-day dated platelet safety, and extend storage to 7 days
  - Pathogen reduction without secondary testing for 5-day platelets

Summary - II

- FDA has presented to the Committee additional considerations:
  - For 5-day platelets: use of the Minimal Proportional Sampling Volume without secondary testing
  - For extension to 7 days
    - Use of Large Volume and Delayed Sampling without secondary testing
    - Secondary testing by culture on Day 4

Questions to the Committee

1. Do the available data support 5-day storage of apheresis platelets without secondary testing if platelets are cultured no sooner than 36 hours post collection with a sampling volume of at least 3.8% of the collection?
2. Do the available data support the following measures to extend dating to day 7?
   a. Culture of apheresis platelets sampled no sooner than 48 hours after collection using a test volume of at least 7% without secondary testing
   b. Repeat culture on Day 4 of apheresis platelets previously tested by a primary culture

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