Bacterial Contamination of Platelets: Strategies to Reduce the Risk

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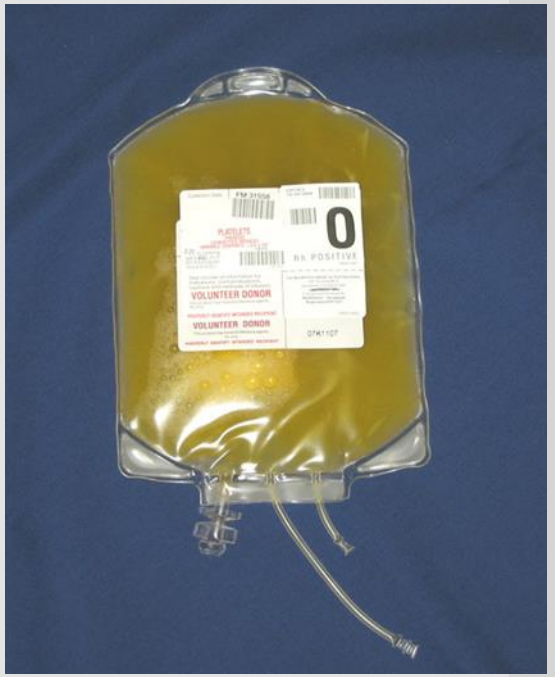


DISCLOSURE

I am an employee of the American Red Cross, which manufacturers standard apheresis platelets as well as pathogen reduced apheresis platelets.

Outline

- Draft Guidance
- Options
  - Primary culture + Secondary culture
  - Primary culture + Rapid bacterial testing
  - Pathogen reduced platelets
  - Large volume delayed sampling
- Our decision at MU, and outcome so far

Background

- March 2016: FDA released Draft Guidance "Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion", which was further updated in December 2018
  - Nonbinding recommendations
  - Applies to all platelet products: apheresis, whole blood derived, pooled, and platelets stored in additive solutions
  - "We recommend that you implement recommendations contained in this guidance ***within 12 months after the final guidance is issued***."
- February 2019: Consolidated Appropriations Act 2019
  - SEC. 768. ***Not later than September 30, 2019***, the Secretary of Health and Human Services shall finalize the draft guidance

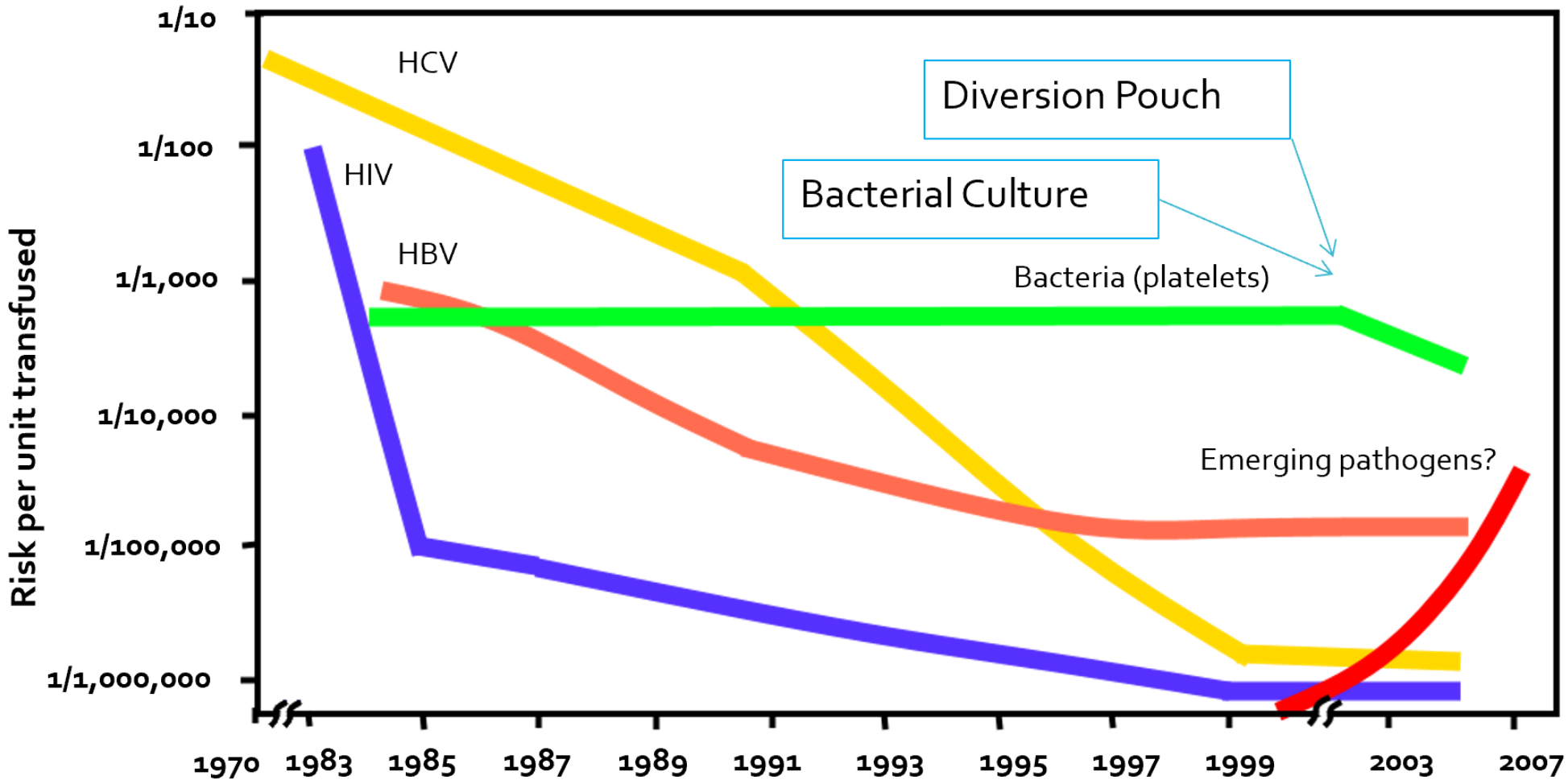
https://www.gmp-compliance.org/gmp-news/fda-draft-guidance-on-the-risk-of-bacterial-contamination-of-blood-platelets

Draft Guidance: Why?

- Room temperature stored platelets are associated with a higher risk of sepsis and fatality than any other component
- Bacterial residual risk per transfused unit is 1:2300
- Fatal reactions continue to occur despite interventions to mitigate risk (primary culture 24 hours from collection, arm cleaning protocols, diversion pouch)

https://www.gmp-compliance.org/gmp-news/fda-draft-guidance-on-the-risk-of-bacterial-contamination-of-blood-platelets
Transfusion 2018;58;938-942

Risks of Transfusion-Transmitted Infections in the United States



Klein HG, et al. Transfusion 2007;47:2338-2347.

Draft Guidance: Why?

- Primary Culture
  - 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 transfusion reactions and 100% of fatalities have occurred with transfusion of day 4 or day 5 platelets

Draft Guidance

Table 1. Summary Table of FDA's Recommendations

Recommendations to control the risk of bacterial contamination in platelets		
Dating	Method	Applicable components
5-day storage	Primary culture + secondary culture (no earlier than Day 3)	• Apheresis • Pre-storage pools
	Primary culture + secondary rapid testing	• Apheresis • Pre-storage pools
	Pathogen Reduction Technology	• Apheresis[3]
7-day storage	Primary culture + secondary culture (no earlier than Day 4)	• Apheresis
	Primary culture + secondary rapid testing	• Apheresis
	Large volume delayed sampling[4]	• Apheresis

https://www.fda.gov/media/119043/download

7 day platelets

- Two medium sized academic medical centers who implemented rapid bacterial testing to extend platelet expiration to 6 or 7 days:
  - Outdate rates went from 5% → 2% and 28% → 14% ($p<0.001$)
  - Although longer storage results in decreased platelet recovery and survival in the platelet transfusion recipient, no observed increase in mean number of platelet units transfused per patient at either hospital

Transfusion 2018;58;938-942

5 day vs 7 day storage

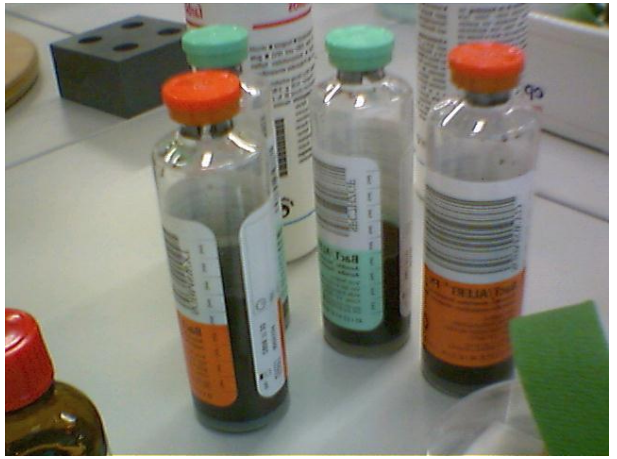
To qualify for 7 day storage:
Must use apheresis platelets collected in 100% plasma in FDA-cleared 7 day platelet storage container, labeled with a requirement to test with an approved bacterial detection device
Culture or rapid bacterial detection devices used to relabel the platelet product with 7 day expiration is a manufacturing procedure requiring registration and blood product listing
Platelets must be tested with the approved bacterial detection device "safety measure" consistent with instructions for use

Transfusion 2016;56;1262-1266.
Transfusion 2018;58;938-942.

Options

Primary Culture

- Already in place; meets draft guidance recommendations when used in conjunction with secondary culture or secondary rapid bacterial testing
- Performed at least 24 hours after collection from the donor by the collection facility
- Should include methods to identify both aerobic and anaerobic organisms
- Use minimum incubation time per manufacturers instructions of your bacterial detection device, or 12 hour minimum if not specified
- Platelets are quarantined until primary culture result is available (minimum 36 hours from collection)



https://commons.m.Wikimedia.org/wiki/File:Blutkulture_-_blood_culture.jpg

Secondary Culture

- Performed no earlier than day 3 for 5 day platelets or day 4 for 7 day platelets
- Recommend using the upper limit of sample volume range permitted by the device's instructions (~8mL) and taken from the main collection
- Inoculate onto aerobic media; consider also performing an anaerobic culture
- Use the minimum incubation period for your device; if no minimum incubation period is specified, establish one in your SOPs

Primary Culture + Secondary Culture

Advantages	Disadvantages
May be the cheapest option, especially if your facility already performs on-site blood cultures	Must create a system to keep track of which units need cultures each day, and which units are in quarantine waiting for culture results
If your facility already performs cultures, no need to implement any new tests or products	Longest quarantine period of all options (36+ hours for primary culture + minimum incubation time for secondary culture), which may negatively impact expiration rates
Allows for 7 day expiration (if you are registered as a manufacturing site and follow requirements), which will reduce expiration rates	False positives would need to be discarded
	Small amount of hands-on tech time to collect sample and perform culture

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 (continues to have initial 36+ hour quarantine from time of collection)
- Small sample volume (500 µL)
- Rapid, ~30 minutes/test and most is hands-off time
- Estimated cost $25-$35/test
- Ability to extend expiration date to 7 days has potential to significant reduce expiration rate and associated costs

Transfusion 2018;58;938-942

Rapid Bacterial Testing

- FDA-cleared rapid bacterial detection devices have an analytical sensitivity of 103 -105 CFU/mL
- Optimally used at least 72 hours after collection
- A study by Jacobs et al demonstrated that rapid testing, performed on the day of transfusion, was able to detect contaminated units that were missed by a culture conducted early in the storage of the units
- This finding provided support for labeling a rapid testing device as a "safety measure." The use of a rapid test labeled as a "safety measure" performed within 24 hours prior to transfusion permits extension of platelet dating up to 7 days

Rapid Test Specificity

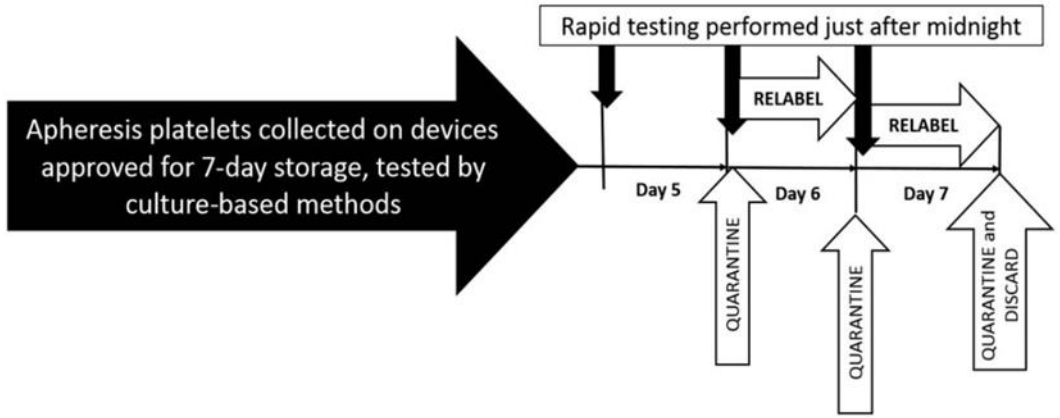


Fig. 2. Timeline for RT testing of APs during Study Period 2. During Study Period 2, all APs underwent an RT just after midnight on Day 5. Day 5 units expired and entered quarantine status at the subsequent midnight (within 24 hours of Day 5 RT). A second RT was performed just after midnight on Day 6. Day 6 units expired and entered quarantine status at the subsequent midnight (within 24 hours of Day 6 RT). A third RT was performed just after midnight on Day 7. Day 7 units expired and entered quarantine status at the subsequent midnight (within 24 hours of Day 7 RT).

- 11,306 rapid tests on 9009 apheresis platelets
  - 1906 underwent testing twice
  - 391 underwent testing 3 times
- No true positives, 0.5% false positives (triplicate negative repeat rapid tests OR positive repeat rapid test with negative culture)

Transfusion 2018; 48;1665-1669.

Rapid Bacterial Testing

- Extension to 7 days associated with significant reduction in platelet expiration rates
- "Implementation of rapid testing is associated with increased work load and costs associated with testing. Both hospitals have developed batch testing schedules to comply with requirements that Day 6 and Day 7 units be tested within 24 hours of dispense. Neither hospital has required additional staffing. There is a low false-positive rate associated with testing (<1%), which also results in additional testing and some unnecessary wastage of units that are repeat testing positive but negative by culture. These limitations should be taken into consideration when investigating the use of rapid testing to enhance apheresis PLT transfusion safety and routinely extend the outdate to 7 days."

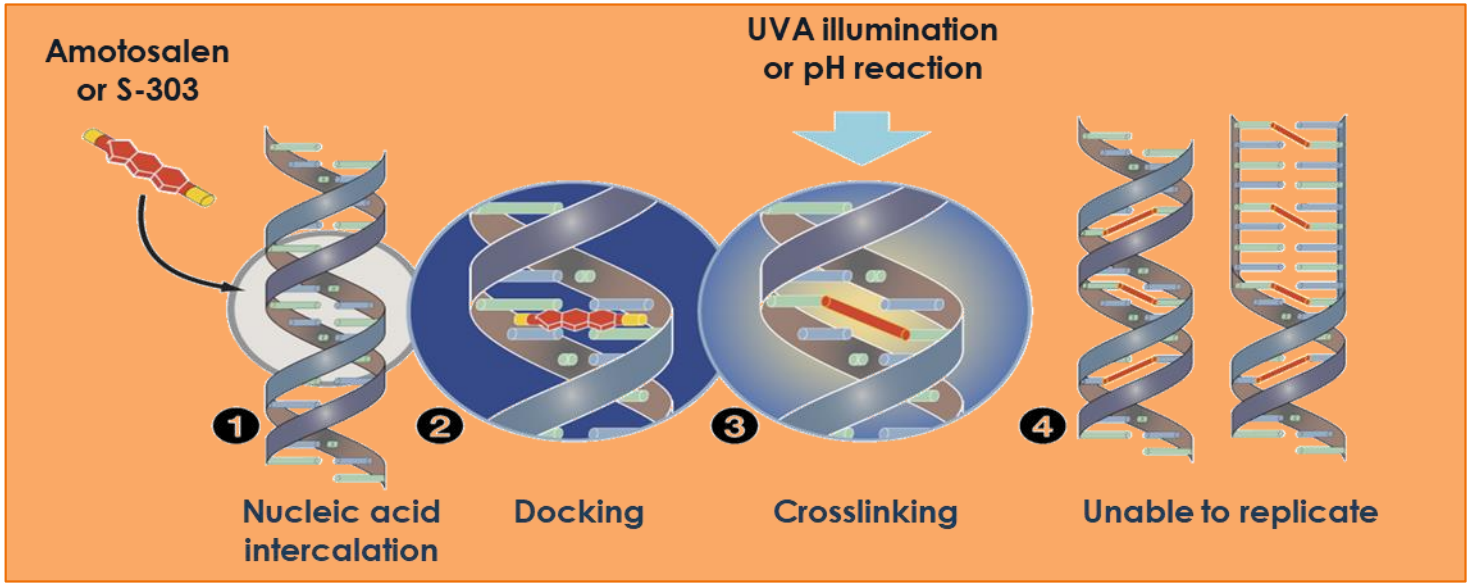
Transfusion 2018;58;938-942

Primary Culture + Rapid Bacterial Test

Advantages	Disadvantages
Low cost, your cost will depend on volume of testing	Must create a system to keep track of which units need testing each day and which units are in quarantine waiting for test results
Rapid test time, easy to perform	Still have 36+ hour quarantine for primary culture + short ~30 minute quarantine for rapid test
Allows for 7 day expiration (if you are registered as a manufacturing site and follow requirements), which will reduce expiration rates and associated costs	False negatives require repeat testing and may result in wasting a small number of units that are truly negative
Sensitive in detecting most bacteria, with low rate of false positives	

Pathogen reduced platelets

- Apheresis collection; psoralen drug is added and then activated with UV light
- Binds to nucleic acids and prevents replication
  - Bacteria, viruses (HIV, Zika, CMV), parasites (malaria, Babesia, Chagas)
  - Emerging organisms?
  - Donor WBCs (no irradiation required for TA-GVHD prevention)
  - No need for primary culture, no 36 hour quarantine after collection



https://www.aabb.org/programs/clinical/Documents/Q-and-A-about-Pathogen-Reduced-Apheresis-Platelet-Components.pdf

Pathogen reduced platelets

- FDA-approved in 2014; in use in Europe for over a decade
- Majority of plasma may be replaced with PAS
  - Associated with reduction in allergic transfusion reactions
- Cost approximately $100/unit on top of base price
- May only be used with 5 day expiration at this time

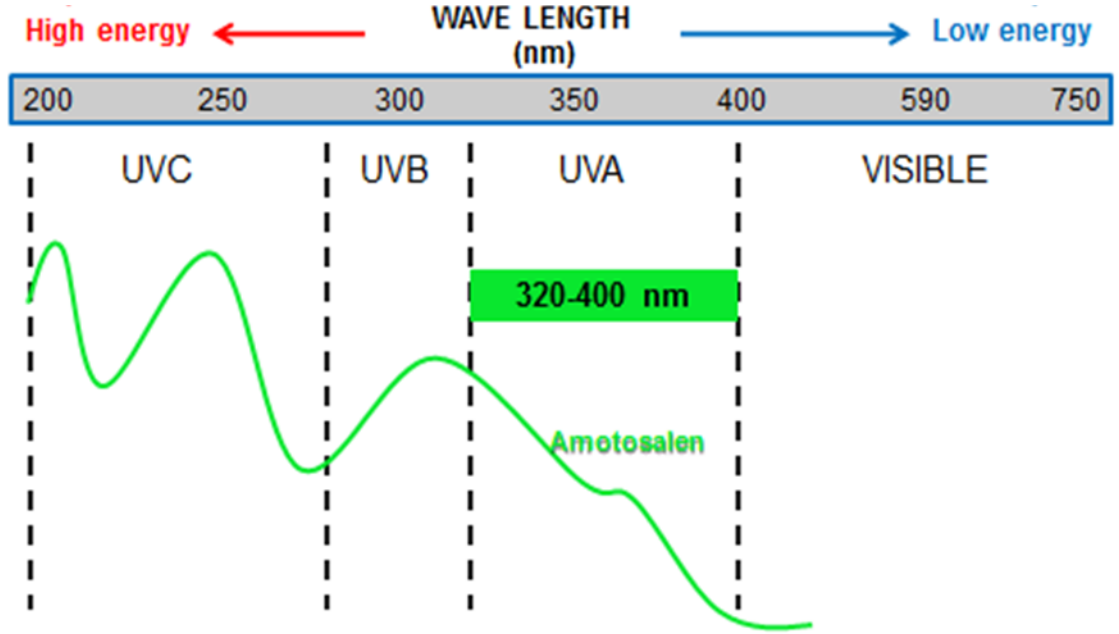
Transfusion transmitted bacterial infection (TTBI)

- Switzerland
  - No cases of sepsis during 130,800 pathogen-reduced platelet transfusions from 2011-2014
- Belgium
  - No TTBIs with more than 150,000 pathogen-reduced platelet products have been transfused since 2009.
  - In the same period, four TTBIs were reported in approximately 186,000 standard platelet transfusions in the Flanders region of Belgium
- France
  - No TTBIs in the 9-year interval from 2007-2015 in the region that transfused only psoralen treated platelets. In contrast, there were 47 cases, including nine fatalities, in parts of France that transfused standard platelets

https://www.aabb.org/programs/clinical/Documents/Q-and-A-about-Pathogen-Reduced-Apheresis-Platelet-Components.pdf

Phototherapy

- Psoralen treated platelets are contraindicated 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



Amotosalen Absorbance: 320-400 nm
Recommended spectrum for intensive phototherapy: 430–490 nm

https://www.aabb.org/programs/clinical/Documents/Q-and-A-about-Pathogen-Reduced-Apheresis-Platelet-Components.pdf

Psoralen toxicity/allergy

- A psoralen medication (amotosalen) is added in conjunction with UVA light exposure. "Although the amotosalen is mostly removed using a compound adsorption device, this creates concern for toxicity in transfusion recipients. However, in-vitro data, animal data, and European hemovigilance data show that the dose of amotosalen components is safe."
- Psoralen treated platelets are contraindicated for patients with a history of allergic reaction to amotosalen or other psoralens. Psoralens are commonly found in the environment: celery, parsley, carrots, dill, lemons, limes, mustard seeds, cilantro

https://www.aabb.org/programs/clinical/Documents/Q-and-A-about-Pathogen-Reduced-Apheresis-Platelet-Components.pdf

Reduced increments?

- SPRINT trial
  - 671 stem cell transplant patients, pathogen reduced vs standard apheresis platelets
  - Mean 1-hour posttransfusion platelet corrected count increment (CCI) was lower with pathogen reduced platelets (11.1×10^3 PCT versus 16.0×10^3 control)
  - Average number of days to next platelet transfusion was lower with pathogen reduced platelets (1.9 days versus 2.4 control)
  - Total number of platelet transfusions was higher with pathogen reduced platelets (8.4 versus 6.2 control) were different ($P < .001$)
  - Transfusion reactions were fewer following pathogen reduced platelets (3.0% PCT versus 4.4% control; $P = .02$)
- Cochrane meta-analysis
  - Corrected count increments (CCIs) at 1 hour and 24 hours were statistically significantly lower after psoralen treated platelet transfusions compared to standard platelets
  - Patients receiving psoralen treated platelets required 7% more platelet transfusions and the transfusion interval between multiple platelet transfusions was shorter than with standard platelets.
  - No differences in mortality, clinically significant bleeding, or severe bleeding between patient groups receiving psoralen treated platelets and those receiving standard platelets.
- The Italian Platelet Technology Assessment Study (IPTAS)
  - No significant difference in absolute risk of grade ≥2 bleeding (22.0% psoralen treated vs 15.9% standard platelets, p=0.16) or in mortality

https://www.aabb.org/programs/clinical/Documents/Q-and-A-about-Pathogen-Reduced-Apheresis-Platelet-Components.pdf

Acute lung injury/ARDS

- Acute respiratory distress syndrome:
  - A warning/precaution in the package insert notes the risk of acute respiratory distress syndrome, which occurred in a randomized trial involving adults
  - Appears to be due to differences in reporting; repeat analysis using standard diagnostic criteria for ALI/ARDS found no significant difference in rates of ARDS
  - The PIPER study is actively evaluating this risk
- Swissmedic Hemovigilance reporting:
  - Incidence of transfusion-related acute lung injury was 1:30,000 after transfusion of standard platelets, compared with 1:24,000 after transfusion with psoralen treated platelets— essentially no difference

https://www.aabb.org/programs/clinical/Documents/Q-and-A-about-Pathogen-Reduced-Apheresis-Platelet-Components.pdf

Pathogen Reduced Platelets

Advantages	Disadvantages
No need to keep track of which units need testing	Highest cost of all options, approximately $100/unit more than base price
No need for primary culture, no quarantine time, no false positives, no hands-on tech time for testing	At this time, no option for 7 day expiration
No need for CMV testing or irradiation, reduction in these costs may partially offset the increased price	Reduced increment, may require additional platelet transfusions
Reduces risk of transfusion-transmitted infection from many bacteria and viruses, potentially including emerging organisms	Ongoing studies looking at incidence of associated respiratory reactions
If manufacturing method uses PAS, reduced incidence of allergic transfusion reactions	

Large Volume Delayed Sampling

- Culture of a large volume of the platelet product (divided into an aerobic and anaerobic bottle) taken 36-48 hours after collection; secondary testing is not performed
- Delayed sampling would allow bacteria already present in the collection to proliferate further, and in conjunction with large volume sampling, could increase the bacterial yield
- Implemented in Québec, Canada and England as measures to allow storage of platelets for up to 7 days, and has been effective in reducing the risk of septic transfusion reaction

https://www.fda.gov/media/114327/download

MU Health
University of Missouri

- MU decision

- Academic Medical Center in Columbia, MO
- Combined 487 acute care beds across 3 hospitals
- Level I Trauma Center
- 15,000 total transfusions annually, ~1100 platelet transfusions
- Largest hospital in Columbia, we accept short-dated products from surrounding smaller facilities
- Not registered for manufacturing with the FDA
- No onsite irradiation
- State funded, Medicare and Medicaid account for about 2/3 of blood unit charges

- Transfusion Committee began discussing rapid bacterial testing vs pathogen reduced platelets in fall 2016, implemented pathogen reduced platelets May 2017
  - Main factors impacting decision:
    - Although more costly, pathogen reduced platelets are less complicated and don't require additional tech time
    - We have a cancer center but no onsite irradiation; pathogen reduced platelets were seen as a benefit from this perspective and the increased cost was partially offset by a reduction in cost of purchasing CMV neg/irradiated units
    - We are not registered with FDA for manufacturing, which was seen as a significant barrier preventing extension to 7 day expiration
  - Concerns:
    - Increased cost, but offset by reduction in CMV negative/irradiated units and possibly reduced expiration rate due to no initial quarantine for primary culture
    - Will it be safe for newborns receiving phototherapy?
    - Will we transfuse more platelet units if the increments are less?
    - What about ARDS?

Staff education

New Psoralen Treated Platelets

This platelet is a psoralen-treated (pathogen-reduced) apheresis platelet. Psoralen Treated platelets offer the following advantages:

- Psoralen Treated platelets are a safe and cost-effective alternative to irradiated/CMV negative products.
- Psoralen Treated platelets reduce the risk of transfusion transmitted bacterial and viral infections with both established and emerging pathogens including HIV, HBV, HCV, Babesia, and Zika.
- Avoidance of cost and complexity of bacterial testing

PSORALEN-TREATED PLATELET ADMINISTRATION

- Platelet dosing and volume of the new psoralen-treated platelets are the same as conventional platelet products.
- Pre-medication and hang time for psoralen-treated platelets are the same as conventional platelet products.
- Patients may receive either conventional platelets or psoralen-treated platelets to fill their transfusion requirements.
- Psoralen-treated platelets can be hung in the same line as conventional platelets.
- All psoralen-treated platelets are leukoreduced.
- As the psoralen-treated platelets do not require irradiation there will **NOT** be a Rad-Sure™ sticker on the bag.

- As the psoralen-treated platelets do not require product to be CMV-, CMV- will **NOT** be indicated on the transfusion tag as a unit antigen.

Unit Antigens: CMV Negative,Irradiated

Phototherapy Interaction?

- Clinical Engineering provided a list of all phototherapy devices in inventory; all (even our older devices) emit wavelengths that are compatible/safe with psoralen treated platelets

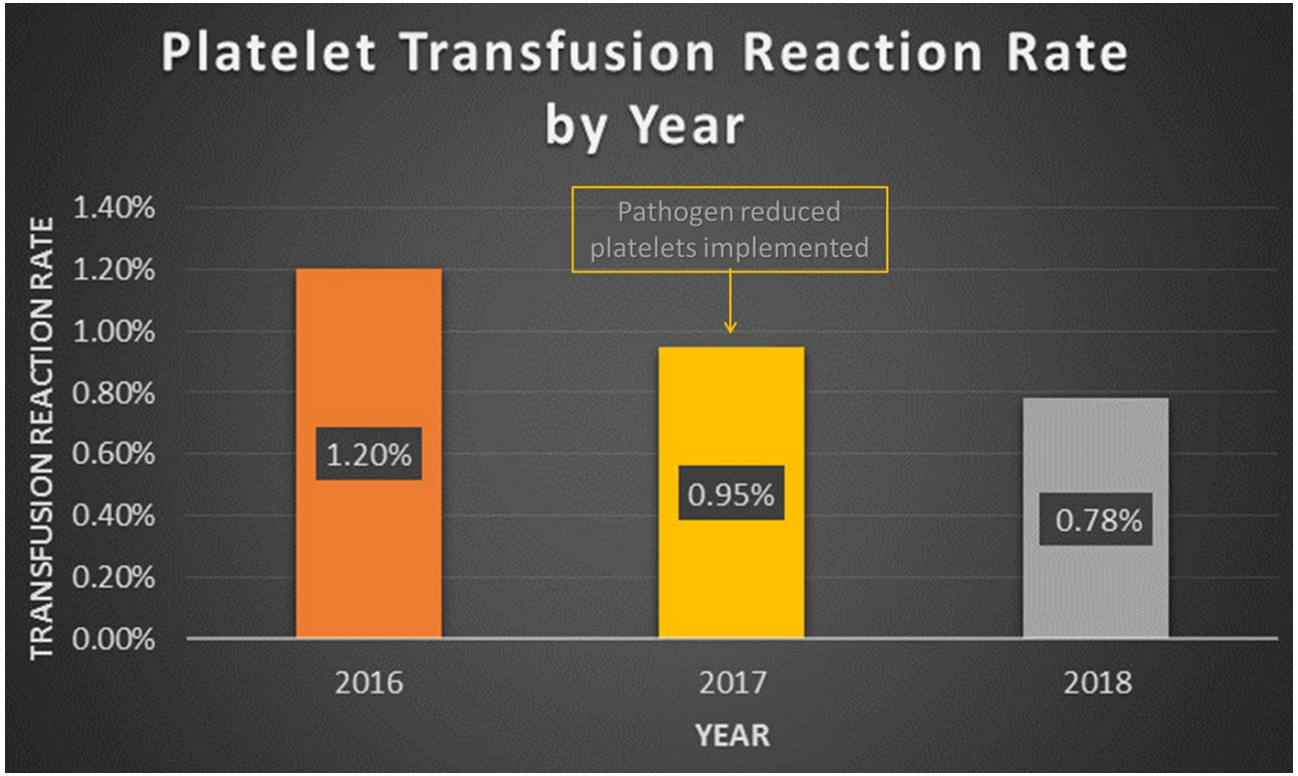
http://www.livestrong.com/article/79481-phototherapy-works-jaundice/

Reduced increments, increased platelet transfusions?

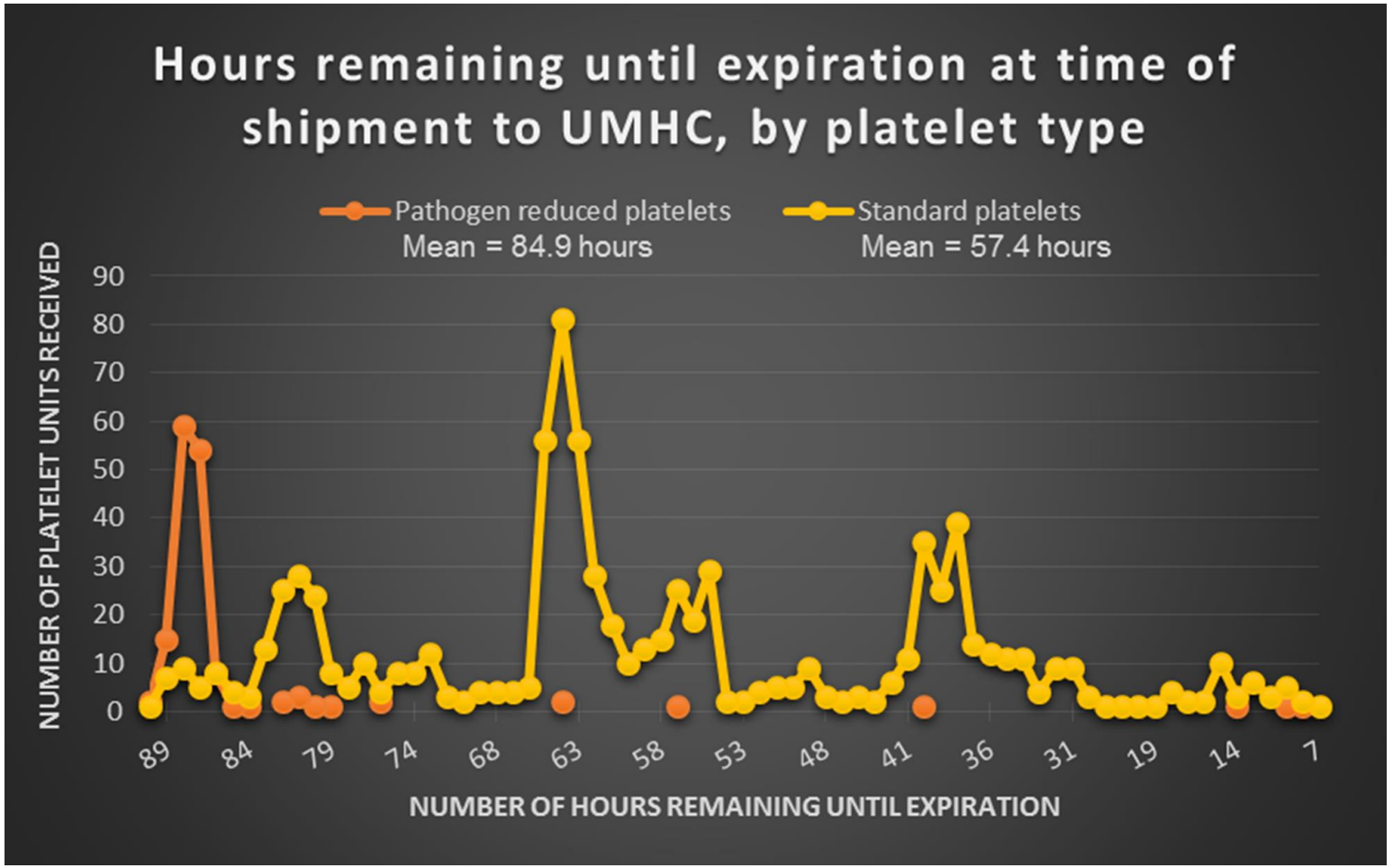
- Educated physicians about this possibility
- Tracked total platelet transfusions before and after implementation, as well as irradiated/CMV negative platelet transfusions
- Total platelet transfusions have trended down since implementation; does not appear to be a clinically significant difference for us

Acute lung injury?

- Educated physicians, with emphasis on hematology/oncology and ICU service lines, regarding potential risks
- No serious transfusion reactions associated with pathogen reduced platelets since implementation
- Total transfusion reaction rate has decreased 35% since implementation

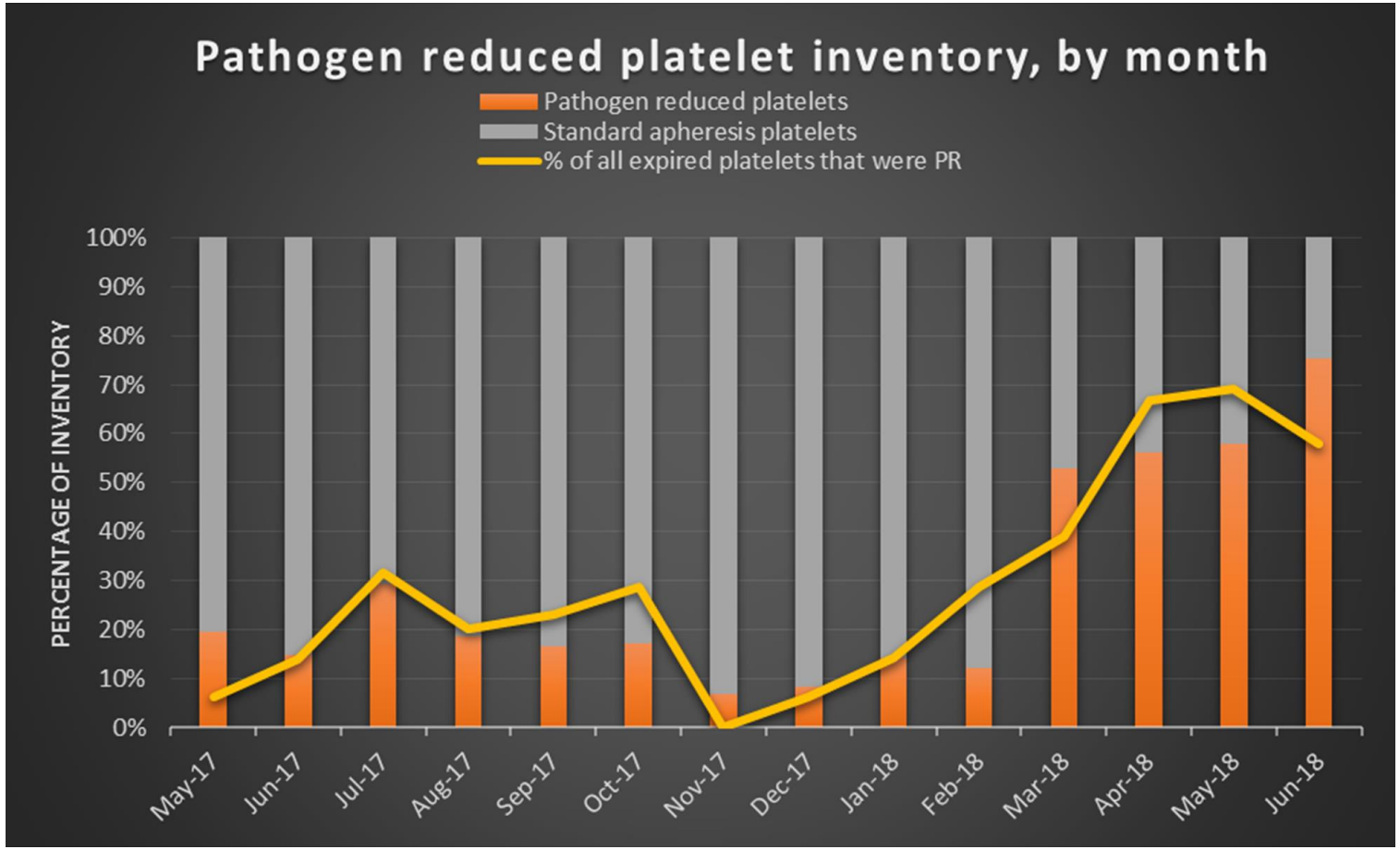


Reduced expiration rate?



Pathogen reduced platelets were received on average more than one full day earlier than standard platelets

Reduced expiration rate?



Overall platelet expiration rate has not improved. The percentage of expired platelets that were PR mirrored the PR inventory each month.

Patient impact

- Overall, pathogen reduced units appear to be safe and effective, and we have not seen an increase in number of platelet units transfused
- Ability to use as an alternative to CMV negative/irradiated has added flexibility since we do not have onsite irradiation
- Costs have increased, partially offset by reduction in purchasing CMV negative irradiated
- Although receiving them earlier due to no initial quarantine, we have not seen a reduction in expiration rate as we were hoping and no option to increase to 7 day expiration at this time

Summary

- Platelet bacterial contamination and fatal septic transfusion reactions continue to occur despite current risk reduction strategies
- FDA final guidance is expected by the end of this month, review carefully to determine final requirements
- Recommended option included in the draft guidance primary culture + secondary culture, primary culture + rapid bacterial test, or pathogen reduced platelets
- Each option has advantages and disadvantages; consider your patient population, volume of platelets transfused, tech workload, costs, and current and predicted expiration rates when making your decision

Questions?