Next steps: Extension of platelet dating and pooling of whole blood-derived platelets

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Background

- Implementation of “limit and detect” requirement
- Culture based tests available
- Impact on useful life of tested platelets
- Impact on platelet volume and dosage
- Regulatory uncertainty
  - Tests approved for QC only
  - Release test needed for proposed products
  - Pathway to safety validation for new products

Extended shelf-life for platelets Background 1

- FDA reduced acceptable storage time from 7 to 5 days in 1986
  - Evidence of increased sepsis from older platelets
  - In-vitro studies
- Platelets available for issue at about 24 hours
  - ID and other testing must be completed before labeling

Extended shelf-life for platelets Background 2

- Culture-based tests require minimum of 24 hours preincubation before culture is initiated
- Growth in culture not detectable before 12-24 hours, or longer
  - Consequently it would appear to be unwise to transfuse platelets until contamination is likely to be detectable
- Available shelf life of platelets is decreased
  - Changes in outdating and/or availability patterns

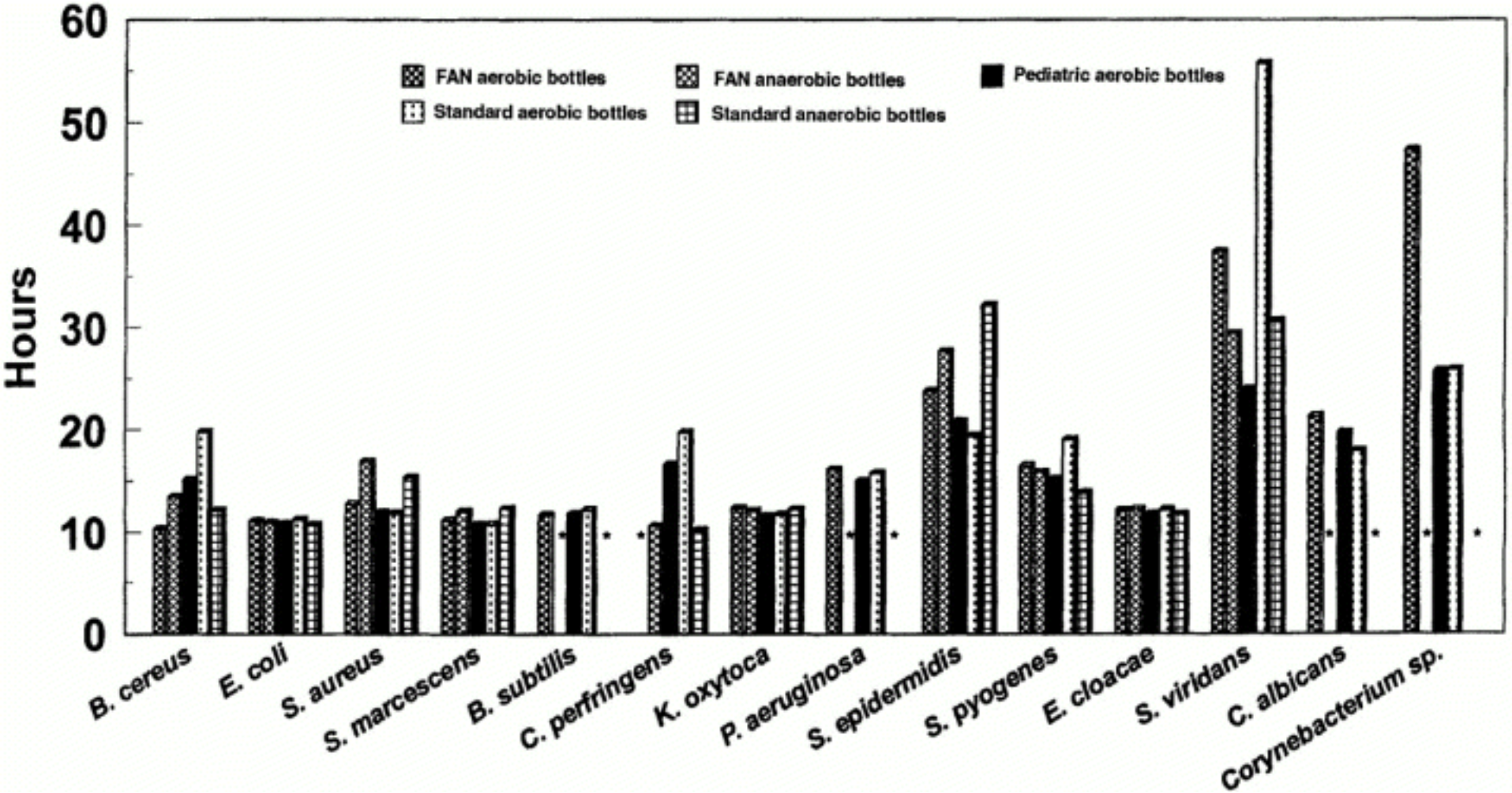
Perceived prerequisites for a 7-day platelet (US)

- Satisfactory maintenance of platelet properties at day 7
  - Scientific acceptance plus regulatory approval of containers
- Maintenance of product bacterial safety
  - Use of a bacterial test approved for release of product
  - Demonstration of equivalence of day 7 and day 5 platelets with respect to bacterial safety

Bacterial test for product release

- No clear guidance
- Product claims
  - Sensitivity, specificity, reproducibility, non-interference
  - Sensitivity usually done with known samples
  - Epidemiologic specificity claim based upon donor population data
- Will there be different standards for bacterial tests
  - e.g. definition of negative predictive value of test
  - If so, by spiking or by population studies?

Spiking studies - data



Brecher et al, Transfusion 2001;41:477-481

7-day platelets

- Current use in Europe
- Limited emergency use in US (AuBuchon)
- BaCon study suggests fatalities early, rather than late in storage for SDPs
  - Extremely limited data, not definitive
- Hong Kong data show additional isolates at day 5 and day 7 but no increment

BaCon Study: summary results

	RBC	SDP	RDP (6/tx)
Distributed	23,711,169	1,804,725	1,033,671
Cases (deaths)	5 (3)	18 (4)	11 (2)
Cases/10^6	0.21	9.98	10.64
Deaths/10^6	0.13	2.22	1.94

Risk factors for fatality

	Fatal (9)	Nonfatal (25)	p values
Gram neg	7 (78%)	7 (28%)	0.009
Plt storage (median)	2.5 days	5 days	0.009
t to rx (median)	23 min	60 min	0.05
Recip age (median)	74 y	20 y	0.05
Volume (median)	86 mL	228 mL	0.02

Characteristics of units associated with fatalities

Product	Contaminant	Store	Endotoxin
SDP	*Gp B Strep.*	4d	NA
SDP	*E. coli*	2d	?
SDP	*P. rettgeri*	3d	9,090 eu
SDP	*E. cloacae*	3d	408,000 eu
RDP	*S. marcescens*	2d	?
RDP	*S. marcescens*	2d	28,600 eu
RBC	*S. epidermidis*	22d	NA
RBC	*S. liquefaciens*	35d	13,000 eu
RBC	*S. liquefaciens*	16d	273,500 eu

Hong Kong data

- 3010 culture negative plts stored 5 days, 3010 stored 7 days
- Recultured at day 6 or 8
- 4 additional positive cultures found in each group (0.133%)
- Staphylococci and *P. acnes*
- 6/8 detectable by Gram stain
- 1 staph at d5, 2 at d7

Lee et al, Transfusion 2003;43:1047-1052

Protocol to assess 7 vs 5 day bacterial contamination

- Based upon outdated SDP
- Suggested n = 50,000 (FDA)
- Bacterial evaluation as current
- Keep in-house outdates (300-400/wk ARC system-wide)
- Bacterial culture at outdate and at day 7
- Aerobic plus anaerobic
- Outcome criteria not defined
- Simultaneous qualification of release test?

Feasibility

- At current rates, > 2years to accumulate study sample using all available outdates in US
- Resource requirements > $5 million
- Regulatory response to outcome unclear
- Cost-benefit unclear, relative to alternate collection strategies, inventory and usage adjustments

Comment

- Effective use of culture-based bacterial tests generate a need for 7-day (apheresis) platelets
- To date, FDA implies that acceptance criteria for bacterial safety of 7-day platelets requires:
  - 1. A test approved for product release
  - 2. 7-day bacterial safety data derived from observations of actual donations
- If these objectives cannot be met, creative alternatives will be required

Pooled, whole-blood derived platelets - background

- Approx 25-30% of therapeutic doses in US are WB-derived
- 100% in some hospitals
- Potential to support temporary or long-term needs that cannot be met by SDPs
  - (manufacturing change: more donors not needed)
- Used in pools of ~ 5 per dose
- US requirements are that platelets must be used within 4 hours of entry into the container (even with use of SCDs)
- Pools must therefore be made in hospital
- Logical preference for blood center pooling

Bacterial testing of WB platelets

- Culture methods problematic
  - Sample volume
  - Relative cost
  - Only for LD products
- Other methods insensitive
  - Dipsticks
  - pH
  - Staining and observation
  - “Swirling” for emergency only

Perceived prerequisites for pooled, WB-derived platelets (US)

- Approved container (at least one manufacturer in development stage)
- In-vitro characteristics maintained
- In-vivo validation (proposed FDA criteria required)
- Resolution of concerns about MLC/cytokine generation in storage
- Integrity of multiple SCDs (BPAC indicated absence of concern)
- Bacterial safety?

Bacterial safety and pooled, WB-derived platelets (US)

- SCD (previously noted)
- Donor exposure same as hospital pools
- Larger volume may permit outgrowth to greater total bacterial load
- Unknown impact of pooling on “self-sterilization”
- Impact of dilution on detectability
- Better availability, size of sample for testing
- Implications for co-components

Outside the US

- Prepooled platelets are the current standard
- Derived from buffy coats
- Product not associated with excess transfusion reactions (cf non-LR in US)
- Bacterially tested with apparent success
- 7-day product routine in some countries at least (eg Netherlands)
- Canada evaluating transition

Prepooled platelets: Open questions

- No guidance on bacterial safety
  - Release test needed?
- Are there regulatory concerns beyond in vitro and in vivo characteristics?
- Hospital response to product?
- Potential for a 7-day product?

Summary

- Bacterial detection is an industry initiative to improve patient safety
- Regulatory approval for a product release test is desirable (currently approved for QC only)
- Optimal achievement of patient safety and adequacy of treatment are best achieved through availability of 7-day platelets and pre-pooled WB-derived platelets
- Equivalent products are available in other countries, with no evidence of failures in safety or efficacy
- There is a need to work with US regulators to develop rational and feasible pathways to validation and approval of these new platelet products