Platelet Additive Solutions (PAS)

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PAS: Definition

- Isotonic, saline based media
  - Citrate: anticoagulant
  - Acetate: fuel of aerobic platelet metabolism

- North America
  - Platelets are predominantly stored in anticoagulated plasma
    - Short shelf life: limited buffering capacity
    - Plasma associated risks

- Advantages of PAS use
  - Patient benefit
  - manufacturing

PAS: Advantages

TABLE I. Advantages of Platelet Additive Solutions

1.	Ability to the formulation to optimize energy metabolism or minimize activation, which could improve viability of Day 5 or allow extended storage to Day 7 or longer
2.	Reduction in plasma volume with anticipated benefits in reduced allergic reactions, and possibly TRALI and ABO mismatched hemolysis
3.	Harvesting of additional plasma for use as a transfusable product or for fractionation. Developments in the automation of platelet manufacture from whole blood or apheresis could incorporate PAS into the manufacturing schema
4.	The PAS milieu could be manipulated to abrogate the deleterious effect of pathogen reduction technology on the platelet storage lesion or facilitate bacterial detection

No published clinical of hemovigilance data to support those theoretical benefits

Current Status of Additive Solutions for Platelets. Hiba Alhumaidan, and Joseph Sweeney*. Journal of Clinical Apheresis 00:000–000 (2012)

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PAS Background

- 1995 PAS II first used in Europe
  - PAS II
    - acetate as a energy source for platelets
    - citrate to prevent clumping and activation
    - sodium chloride for osmolarity.
- 2007 PAS III approved in Europe (stand-alone)
  - PAS III (InterSol®) is similar to PAS II
    - addition of phosphate: pH buffer
  - 2002 as part of the Intercept pathogen reduction system

PAS Background

- PAS III used in a fixed ratio with plasma
  - 65% PAS and 35% plasma
- PAS III has no pharmacologic effect in vivo
- Developed to:
  - Increase platelet viability during storage
  - Minimize plasma loss/optimize components donated
  - Reduce plasma-related transfusion rxs
- Clinical efficacy of PAS units vs. plasma has been evaluated
  - no differences in bleeding outcomes

PAS III

- FDA approved 12/2009
  - PAS III; PAS-C; InterSol (Fenwal/Baxter, Lake Zurich, IL)
- Approved only to be used w/ AMICUS apheresis syst. (Fenwal/Baxter)
  - leukocyte-reduced apheresis units
- PAS apheresis platelets: 65% PAS and 35% plasma
  - Not yet available in the SE ARC system
- Stored up to 5 days at 20-24 ^{o}C with continuous agitation
- Fenwal has validated BacT/ALERT use w/ PAS platelet units
- ICCBBA (manages/develops/licenses ISBT 128)
  - has added PAS to ISBT 128 product codes

Platelet Metabolism

- Platelets derive energy from
  - glucose oxidation through glycolysis (cytoplasm)
    - lactic acid
  - β-oxidation of long-chain fatty acids (mitochondria)
    - coupled with oxidative phosphorylation (very efficient)
    - requires O_2
    - gas permeability is critical for O_2 and CO_2 diffusion (gas permeable container)
- Storage associated pH decline (<6.2)
  - Platelet viability becomes severely compromised
    - Buffer systems: gluconate, phosphate, bicarbonate

Platelet Metabolism

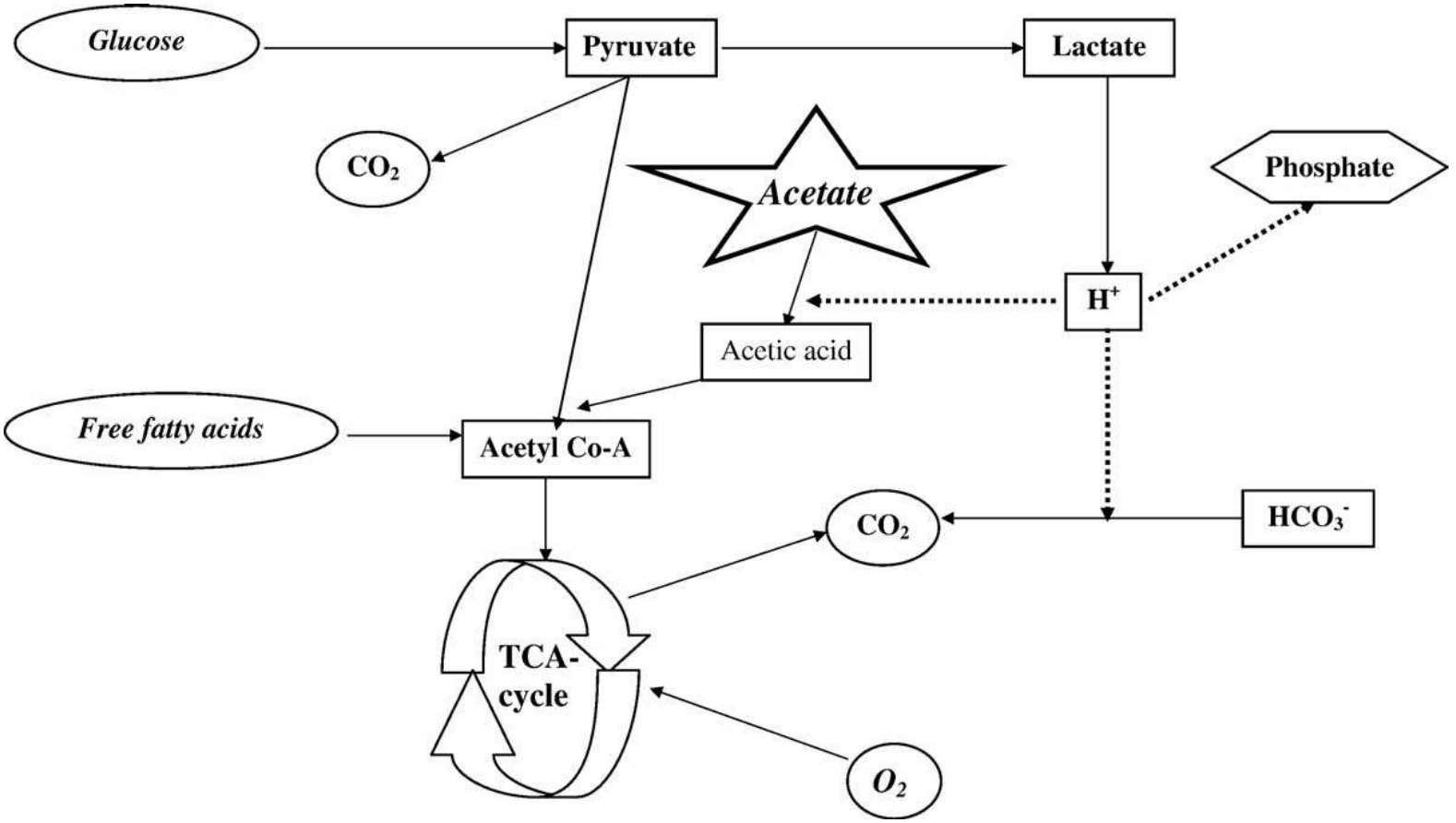

Fig 1. Metabolic pathways of PLTs with a focus on the role of acetate and the buffering of hydrogen ions derived from anaerobic glycolysis. Beside free fatty acids, acetate can serve as substrate for the oxidative metabolism in the tricarboxylic acid cycle. Furthermore, acetate can act as an alternate buffer to HCO3 and phosphate (n n na).

Transfusion Medicine Reviews, Vol 20, No 2 (April), 2006: pp 158-164

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Platelet Metabolism

- Glucose is essential
  - Supplied by the retained plasma
  - Difficult to replace with PAS
    - Caramelizes with sterilization under physiologic pH
  - Without agitation (e.g. manufacture and shipping)
    - Anaerobic glycolysis increases
      - pH decreases: buffer system needed
  - Glucose containing PAS
    - Allows for greater plasma volume removal

Clinical Efficacy

- **2 studies with PAS II**
  - **decreased CCI for the PAS-stored platelets versus platelets in plasma**
  - **Interval between platelet transfusions, # of transfusions, and # or severity of bleeding episodes not statistically different**

de Wildt-Eggen J, Nauta S, Schrijver JG, et al. Reactions and platelet increments after transfusion of platelet concentrates in plasma or an additive solution: A prospective, randomized study. **Transfusion 2000;40:398-403.**

Kerkhoffs JL, Eikenboom JC, Schipperus MS, et al. A multicenter randomized study of the efficacy of transfusion with platelets stored in platelet additive solution II versus plasma. **Blood 2006;108:3210-5.**

- **1 study with PAS III**
  - **compared platelets in PAS III, platelets in plasma, and platelets in PAS-C treated with the INTERCEPT pathogen reduction technology (PR-PAS-C)**
    - **CCI not statistically different between PAS III and plasma units**
    - **Interval between platelet transfusions, # of transfusions, and # or severity of bleeding episodes not statistically different**

Kerkhoffs JL, van Putten WL, Novotny VM, et al. Dutch-Belgian HOVON cooperative group. Clinical effectiveness of leucoreduced, pooled donor platelet concentrates, stored in plasma or additive solution with and without pathogen reduction. ***Br J Haem 2010;150:209-17****.*

- **Unclear if different results are due to different chemistry of PAS II and PAS III**

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Transfusion Reactions

- **Incidence of transfusion rxs may be reduced**

•3 studies w/ PAS II showed decreased incidence of allergic rxs

de Wildt-Eggen J, Nauta S, Schrijver JG, et al. Reactions and platelet increments after transfusion of platelet concentrates in plasma or an additive solution: A prospective, randomized study. ***Transfusion 2000;40:398-403.***

Kerkhoffs JL, Eikenboom JC, Schipperus MS, et al. A multicenter randomized study of the efficacy of transfusion with platelets stored in platelet additive solution II versus plasma. ***Blood 2006;108:3210-5.***

Herve F, Tardivel R, Semana G, Andreu G. Large scale use of platelet additive solutions (PAS) reduces allergic type transfusion adverse events. ***Vox Sang 2007;93 (Suppl): 267.***

•1 randomized control trial with PAS III showed no difference

Kerkhoffs JL, van Putten WL, Novotny VM, et al. Dutch-Belgian HOVON cooperative group. Clinical effectiveness of leucoreduced, pooled donor platelet concentrates, stored in plasma or additive solution with and without pathogen reduction. ***Br J Haem 2010;150:209-17.***

•2 large observational hemovigilance studies w/ PAS III showed decreased incidence of transf. rxs

Osselear JC, Messe N, Hervig T, Bueno J, Castro E, Espinosa A, Accorsi P, Junge K, Jacquet M, Flament J, Corash L. A prospective observational cohort safety study of 5106 platelet transfusions with components prepared with photochemical pathogen inactivation treatment. ***Transfusion 2008;48:1061-71.***

Osselear JC, Cazaneve JP, Lambermont M, Garraud O, Hidajat M, Barbolla L, Tardival R, Defoin L, Waller C, Mendekl I, Raidot JP, Kandel G, Demeuter R, Fabigli P, DEhenau D, Arroyo JL, Padron F, Gouezec H, Corral M, Jacquet M, Sundin D, Lin L, Corash L. An active hemovigilance programme characterizing the safety profile of 7437 platelet transfusions prepared with amotosalen photochemical treatment. ***Vox Sang 2008;94:315-23.***

PAS: Formulations

TABLE II. Approximate Formulations of Additive Solutions

Chemical	PAS-I plasmalyte	PAS-II (T-Sol)	PAS-III (Intersol)	PAS-IIIM SSP$^+$	ComposolPAS-G	M-Sol
NaCl (mM)	90	116	77	69	90	110
NaAcetate (mM)	27	30	30	30	27	15
NaCitrate (mM)	–	10	10	10	11	10
KCl (mM)	5	–	–	5	5	5
Mg Cl_2 (mM)	3	–	–	1.5	1.5	3
Phosphate (mM)	–	–	26	26	–	4
Na Gluconate (mM)	23	–	–	–	23	–
Glucose (mM)	–	–	–	–	–	30
$NaHCO_3$ (mM)	–	–	–	–	–	12

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For Transfusion Services and Blood Centers

- Platelet collection procedure and storage container is the same
- Platelet counts and storage fluid volumes are not affected
- Irradiation and volume-reduction are not affected
- Variation in color is expected
    - Platelets in PAS may be lighter in color
- Swirl can still be detected.
- PAS does not contain mannitol, adenine or dextrose
    - Does not have same concerns as some RBCs additive solutions
    - Review of contents should be performed w/ neonatologists
        - address any potential concerns
- Discuss use PAS w/ Transfusion Committees prior to implementing its use

PAS Summary

- Additional PASs under development
- Platelets in PAS have equivalent efficacy compared to standard units
    - Clinical outcome: bleeding
- PAS units appear to have lower risk for allergic transfusion rxs
- Reduced amount of plasma required for storage
    - Coag factor values (in the AABB *Technical Manual*) will be reduced
    - Reduced risk of hemolytic transfusion rxs
        - due to ABO incompatibility
- PAS should not be directly infused into a patient

Thank you.