BLOOD BULLETIN

JULY 2016

PROVIDED BY YOUR INDEPENDENT,
NONPROFIT COMMUNITY BLOOD CENTER
In conjunction with America's Blood Centers ®

San Diego Blood Bank

Pathogen Reduction of Transfusable Blood Products

By: Vincent Lee, OMS I, Western University of Health Sciences, College of Osteopathic Medicine of the Pacific, and Minh-Ha Tran, DO, Associate Clinical Professor of Pathology & Medicine, University of California, Irvine; Associate Medical Director, Transfusion Medicine Services, UC Irvine Health. The authors disclose no conflicts of interest.

Introduction: Current practices aimed at reducing the risks for transfusion-transmitted diseases (TTDs) and certain other transfusion complications require the careful recruitment and behavioral screening of volunteer donors, testing for evidence of blood-borne pathogens, and use of good manufacturing practice-compliant systems to avoid the collection and distribution of unacceptable blood components. Despite these efforts, however, numerous TTDs – especially emerging agents for which donor screening is not available – continue to threaten blood safety. Pathogen reduction (PR) encompasses a number of processes that render most blood-borne pathogens non-infectious (and also inactivate residual white blood cells).

Key Points

- Pathogen reduction (PR) proactively reduces the risk of transfusion-transmitted diseases, including that of many emerging infectious diseases.
- Bleeding outcomes have been comparable between patients receiving PR-treated vs. standard platelets and plasma (potential exception: massively bleeding patients).
- PR is an effective alternative to irradiation for mitigation of transfusion-associated graft-vs.-host disease.
- Rates of febrile nonhemolytic and allergic transfusion reactions appear to be lower with PR-treated platelets; solvent-detergent-treated pooled plasma has been associated with reduced TRALI risk.
- PR of whole blood and RBCs is not yet approved.

Background: Per-unit risks (and test-negative window periods) for the most serious TTDs have fallen substantially in recent decades – e.g., to 1:1,467,000 (9.0-to-9.1 days) for HIV, 1:1,149,000 (7.4 days) for hepatitis C virus (HCV), and 1:843,000-1:1,208,000 (18.0-to-26.5 days) for hepatitis B virus (HBV).[1-3] Still, TTD threats persist, especially for emerging agents such as *Babesia* and Zika virus.

Platelet transfusion-associated septic reactions also remain problematic, because the room temperature storage of these products (i.e. compared to the refrigerated conditions used for red blood cells) favors bacterial growth. In North America, bacterial culture is done on platelet units no sooner than 24 hours after collection, after which products are often held for an additional incubation interval of 12-24 hours prior to their release, thereby delaying their availability.[2] Despite this, however, active surveillance has found contamination in 1:2,571 platelet doses transfused and a septic reaction rate of 1:10,288 [4] (note: the latter must be multiplied by the number of units to which a patient is exposed to estimate per-patient risk). Moreover, the estimated mortality rate is 1 per 500,000 platelet transfusions.[5]

Pathogen Reduction: PR constitutes a shift from a reactive strategy toward a more proactive one. Available technologies consist primarily of chemical inactivation (e.g., solvent-detergent treatment = SDT) and photochemical treatment (PCT).

SDT, used exclusively on plasma products, lyses cell membranes and viral envelopes, leading to >5.4-6.0 log reductions for sensitive pathogens.[6] The SDT plasma product Octaplas (Octapharma AG, Switzerland) is manufactured using pools of human donor plasma obtained from 630-1,520 individual donors.[7] The dilutional effect associated with such pooling significantly reduces the per-dose impact of any putative donor leukocyte antibodies, such as those that cause TRALI (transfusion-related acute lung injury). French hemovigilance data from 2007-2008 identified no TRALI cases associated with the transfusion of more than 200,000 units of SDT plasma[8,9] treated with FDA-licensed Octaplas in January 2013, but use of this product remains limited, due primarily to cost.

PCT methods, applicable to plasma *and* platelet products, include INTERCEPT (Cerus Corporation, Concord, CA, USA) and Mirasol (Terumo BCT, Lakewood, CO, USA).The former uses a psoralen compound (amotosalen) that is activated by UV-A light. The latter uses riboflavin exposed to broad spectrum UV light. Both lead to irreversible damage to nucleic acids and inactivation of microorganisms and leukocytes.

The SPRINT trial,[10] using INTERCEPT platelets, demonstrated comparable rates of WHO grade 2-4 bleeding in patients transfused with PR vs. conventional platelets (Grade 2 bleeding: 58.5% vs. 57.5%, respectively; grade 3/4 bleeding: 4.1% vs. 6.1%; p = 0.001) and a slight reduction in the rates of transfusion reactions (manifested "primarily [by] fever, chills, urticaria, or rash") in the PR group compared to

the control (3.0 vs. 4.4%; p = 0.02). The experimental group experienced lower 1- and 24-hour corrected count increments and the need for greater numbers of transfusions (averaging 8.4 vs. 6.2 units per patient for PR versus control products, respectively; p<0.001).[10] In December 2014, FDA approved the INTERCEPT Blood Systems for both platelets and plasma. Further work is being done on Mirasol platelets and plasma, which are CE-marked and used in Europe and other parts of the world, but have not yet received U.S. licensure.

Existing PR methods inactivate residual leukocytes (i.e., in addition to most microbes) contained within platelet components and obviate the need for x-ray or gamma irradiation to prevent transfusion-associated graft-vs.-host disease.[11] Moreover, platelets treated via available PR methods have been protected from bacteria, do not require bacterial screening and may, under appropriate conditions, be stored for up to 7 days.[12] A future advantage of PR is the potential to eliminate TTD tests for emerging agents (e.g., for dengue and Zika virus).[12]

In a real-world report of the introduction of INTERCEPT platelets, overall platelet production costs increased by 85.5%, of which 69.6% was comprised by INTERCEPT processing. Reduced expiration of platelet products (associated with 7-day storage) and other savings reduced the overall increase to 71.7%.[13] Also, existing PR methods in general may be less efficacious against certain very high titer agents, like HBV, and intrinsically resistant to pathogens like prions, hepatitis A virus, parvovirus B19, and bacterial spores.[6,14] Moreover, questions still must be answered about the extent to which the use of PR-treated platelets may, or may not, contribute to the need for increased numbers of platelet and RBC transfusions on a per-patient basis.[15] This is exemplified by a recent, controversial, commentary alleging a possible increased mortality associated with the use of standard doses of PR-treated platelets and plasma during the transfusion management of massively bleeding patients.[16]

The more efficiencies gained from PR, the greater the incentive will be to adopt this strategy. However, the motivation of some blood centers and many hospitals to implement use of PR-treated components may be offset by concerns about increased (and suboptimally reimbursed) costs and reduced operational efficiencies. Regarding the latter, absent the ability to apply PR to triple plateletpheresis collections, there is much discussion about the problematic impact PR will have – until further refinements are approved – on reducing success rates for multi-product platelet collections.

Lastly, manufacturers continue to work on the "holy grail" of PR – i.e., its application to whole blood and/or red blood cells that constitute the large majority of transfusions. The primary challenge is to identify processes that will work in the opaque, i.e. more-light resistant, milieu of these blood components. A landmark randomized trial has demonstrated that the Mirasol whole blood system can reduce transfusion-transmitted malaria by 90% in sub-Saharan Africa.[17]

Conclusions: PR technology effectively reduces the residual burden of most pathogens in platelets and plasma. Currently, no methods are approved in the U.S. for the treatment of whole blood or red blood cell components. The benefits of PR should be balanced against institutional, regional, and societal costs associated with implementation. More blood centers are developing their capacity to manufacture PR components – especially platelets. Time will tell, however, how rapidly hospitals and clinicians will drive the demand for this capacity.

References

1. Zou S, Dorsey KA, Notari EP, et al. Prevalence, incidence, and residual risk of human immunodeficiency virus and hepatitis C virus infections among United States blood donors since the introduction of nucleic acid testing. Transfusion. 2010;50:1495-1504.
2. Galel SA. Infectious Disease Screening. In: Technical Manual, 18th Eds. Fung MK, Grossman BJ, Hillyer CD, Westhoff CM 2014, AABB.
3. Stramer SL, Notari EP, Krysztof DE, Dodd RY. Hepatitis B virus testing by mini-pool nucleic acid testing: does it improve blood safety? Transfusion. 2013;53:2449-58.
4. Hong H, Xiao W, Lazarus HM et al. Detection of septic transfusion reactions to platelet transfusions by active and passive surveillance. Blood. 2016;127:496-502.
5. Eder AF, Kennedy JM, Dy BA, et al. Limiting and detecting bacterial contamination of apheresis platelets: in-line diversion and increased culture volume improve component safety. Transfusion. 2009;49:1554-63.
6. Stramer SL, Hollinger FB, Katz LM, Kleinman S, Metzel PS, Gregory KR, Dodd RY. Emerging infectious disease agents and their potential threat to transfusion safety. Transfusion. 2009;49:1s-29s.
7. Octaplas Package Insert. Octapharma. 2014. http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/UCM336161.pdf (accessed June 26, 2016).
8. Sachs UJ, Kauschat D, Bein G. White blood cell-reactive antibodies are undetectable in solvent/detergent plasma. Transfusion. 2005;45:1628-31.
9. Ozier Y, Muller JY, Mertes PM, et al. Transfusion-related acute lung injury: reports to the French Hemovigilance Network 2007 through 2008. Transfusion. 2011;51:2102-10.
10. McCullough J, Vesole DH, Benjamin RJ, et al. Therapeutic efficacy and safety of platelets treated with a photochemical process for pathogen inactivation: the SPRINT Trial. Blood. 2004;104:1534-41.
11. Fast LD. Developments in the prevention of transfusion-associated graft-versus-host disease. Br J Haematol. 2012;158:563-8.
12. McCullough J, Goldfinger D, Gorlin J, et al. Cost implications of implementation of pathogen-inactivated platelets. Transfusion. 2015;55;2312–2320.
13. Girona-Llobera E, Jimenez-Marco T, Galmes-Trueba A, Muncunill J, Serret C, Serra N, Sedeno M. Reducing the financial impact of pathogen inactivation technology for platelet components: our experience. Transfusion. 2014;54:158-68.
14. Prowse CV, Component pathogen inactivation: a critical review. Vox Sanguinis. 2013;104:183-99.
15. Rebulla P, Vaglio S, Aprili G, et al. Clinical efficacy and safety of platelets in additive solution treated with two commercial pathogen reduction technologies. Transfusion. 2015;55(S3): 3A-4A.
16. Hess JR, Pagano MB, Barbeau JD, Johannson PI. Will pathogen reduction of blood components harm more people than it helps in developed countries? Transfusion. 2016; 56;1236–41.
17. Allain J-P, Owusu-Ofori AK, Assennato SM, *et al*. Effect of Plasmodium inactivation in whole blood on the incidence of blood transfusion-transmitted malaria in endemic regions: the African Investigation of the Mirasol System (AIMS) randomised controlled trial. *Lancet*. 2016. 387:1753-61.

America's Blood Centers® It's About Life.

Blood Bulletin is issued periodically by America's Blood Centers. Publication Committee Chair: Chris Gresens, MD. The opinions expressed herein are opinions only and should not be construed as recommendations or standards of ABC, ABC SMT Committee, or its board of trustees. Publication Office: 725 15th St., NW, Suite 700, Washington, DC 20005. Tel: (202) 393-5725; Fax: (202) 393-1282; E-mail: abc@americasblood.org.