Pathogen inactivation: a new paradigm for blood safety

In this issue of TRANSFUSION, Klein and colleagues[1] report the results of a consensus conference on pathogen inactivation (PI) sponsored by the Canadian Blood Service and Héma-Québec. The organizers of the conference have done an outstanding job of selecting the panel and posing questions that nicely frame the issues regarding PI. The panel has written an outstanding report that will be of interest to all of us in transfusion medicine and of great help in considering the future of PI. In this editorial, I will review and discuss some of the panel's findings and place them into context with my assessment of the present paradigm for minimizing transfusion-transmitted infections and the current status of PI. I will also provide some additional perspective to some of the issues that the panel identified in their extensive consideration of this evolving field and suggest that these issues will require extensive discussion with many stakeholders. Finally, I will offer my conclusions about where we need to move in the future.

SHORTCOMINGS OF THE PRESENT PARADIGM FOR MINIMIZING TRANSFUSION-TRANSMITTED INFECTIONS

Since the onset of the AIDS epidemic, the panel noted dramatic improvements that have been made in blood safety. These have come from new tests for transmissible diseases; seven have been introduced in the United States since 1985, along with many additional questions in the donor medical history. Current rates of posttransfusion infection from the most well-known agents are extremely low and range from 1 in 900,000 to 7.8 million (human immunodeficiency virus [HIV]) units of blood to 1 in 77,000 to 1.1 million (hepatitis B virus [HBV]).[1,2] On the basis of this background of data, the panel's position was that PI cannot be recommended for introduction "based on the relatively low rates of existing infectious transfusion-related complications *alone*" (italics are this author's). This conclusion illustrates that our present paradigm for the prevention of transfusion-transmissible infections has served us and patients extremely well over the past two decades. The issue then becomes whether this paradigm can be sustained in the future and can continue to be the best approach to maximize blood safety.

Our present paradigm for preventing transfusion-transmitted infections has several shortcomings including:

1. It applies only to known pathogens and transfusion-transmitted infections. Thus, the paradigm accepts that new agents will be allowed to enter the blood supply and our response will be reactive after the problem becomes apparent. West Nile virus (WNV) is the most recent example of the reactionary nature of our present paradigm. The blood banking and/or transfusion medicine community, industry, and regulators worked together to respond to the epidemic with unprecedented speed.[3] As many as several thousand patients may have been infected, however, and in one report 7 of 23 infected patients died.[4] Another example of a new infectious agent entering the blood supply is the Chikungunya virus epidemic that occurred in the island of Le Reunion,[5] a French department in the Indian Ocean. The outbreak was due to a new variant that may have enabled the virus to adapt to a new mosquito vector.[5] Because a large proportion of the population was infected, blood donation was halted on the island, red cells (RBCs) and plasma were shipped in, and PI procedures were put in place for island platelet (PLT) donations. At least 37 cases of infection by this virus are now known in the United States, although these cases occurred in travelers returning from epidemic areas.[6]
2. The current paradigm does not even prevent all known transfusion-transmitted infections. A test has recently become available for Chagas disease, but no practical steps are used to prevent babesiosis, Dengue, HHV-8, babesia, and others. Attempting to prevent transfusion-transmitted malaria by travel history is ineffective and defers many otherwise suitable donors. Cytomegalovirus (CMV) infection is another example of the shortcomings of our current paradigm. Even after leukodepletion or CMV antibody screening of donated blood, transfusion-transmitted CMV occurs.[7]
3. Because our present paradigm is reactive to the occurrence of new infectious agents, it accepts that some patients will be harmed before steps can be taken to minimize transmission of the agent. WNV and patients infected, some fatally, are the most recent examples of this shortcoming.

Disclosure: The author discloses a financial relationship with both Cerus and Navigant Corporations through service on advisory boards or committees and through receipt of research funds in the past.

TRANSFUSION 2007;47:2180-2184.

4. Current methods to detect and/or prevent transfusion of bacterially contaminated products are inadequate. The AABB standard requiring methods to reduce bacterial contamination of PLTs led to the introduction of testing and has reduced the danger of transfusion-transmitted sepsis. The available test methods, however, are not really suitable for this purpose and even after introduction of screening, transfusion-related septic reactions continue to occur.[1,8]
5. Many donors whose blood does not pose a risk to patients are temporarily or permanently deferred because of the lack of precision of the present screening tests or deferral criteria. The best examples of this paradigm deficiency are donor history questions regarding travel to malaria areas and travel to the United Kingdom and France for new variant CJD.

The panel recognized these shortcomings, particularly the threat of emerging viruses, and recommended "that PI should be implemented when a feasible and safe method to inactivate a broad spectrum of infectious agents is available."[1] The panel based this recommendation in part on the precautionary principle. This principle recommends that when a threat to the public health can be reasonably predicted, a proactive approach should be taken and that the burden of proof is on those who advocate a restrictive approach.

CURRENT STATUS OF PI

Methods

Solvent/detergent (S/D) treatment has been used for years in the manufacture of plasma derivatives. S/D is also used to prepare individual units of frozen plasma from pools of approximately 2500 donors. Although this product is no longer available in the United States, it is used in some other countries primarily in Europe. S/D inactivates only lipid envelop viruses. Methylene blue can be added to plasma and, when exposed to visible light, inactivates most viruses and bacteria. Methylene blue treatment of plasma is used in some European countries.

Several other methods target and damage DNA or RNA thus preventing organisms from reproducing. The three that are most highly developed involve the use of riboflavin (vitamin B2) and UV light for PLTs, plasma, and RBCs (Navigant Corp.), the psoralen compound amotosalen and UV light for PLTs and plasma (Cerus Corp.), and a bifunctional alkylator for PI of RBCs (Cerus Corp.). Details of these methods can be found in recent reviews.[9,10]

Toxicity of compounds used for PI

The safety profiles of these compounds have been studied in ways consistent with general pharmacology[1,11] and are within safety limits. Although the alkylator compound used for RBC PI is similar to alkylators used in chemotherapy, it appears to have a satisfactory safety profile.[10]

Pathogens inactivated

Amotosalen, riboflavin, and the alkylator inactivate a wide variety of pathogens at up to 10^6 or more particles per milliliter.[9,10] The extent to which this level of PI reverses the threat from all pathogens that would be expected in an apparently healthy blood donor is difficult to conclude. Most commercial assays detect both full-length and incomplete noninfectious particles, making it difficult to determine the true level of infectivity in apparently healthy blood donors. For most transfusion-transmitted infections, the level of measurable particles in apparently healthy individuals is below the extent of inactivation obtained in vitro. PI with the amotosalen method effectively inactivated HBV and hepatitis C virus (HCV) in an animal model; and other studies suggest the efficacy of PI for other agents with other compounds.[12] It appears that these three compounds are very effective inactivating transfusion-transmitted pathogens including those for which no prevention strategy is currently in place.

Graft-versus-host disease

Because the PI process damages DNA and prevents the replication of nucleic acids, the process prevents replication of lymphocytes in treated blood components.[13,14] Thus, PI-treated blood components should not cause transfusion-related graft-versus-host disease (GVHD). This promise has been confirmed clinically in some centers in Europe that have discontinued irradiating PI PLTs produced with the amotosalen method without observed transfusion-related GVHD.[13,15]

Present use of PI worldwide

There is extensive literature that documents the in vitro and animal studies of cell and protein function that have occurred with PI compounds, a wide variety of in vivo Phase I studies, and a number of clinical trials of PI that have been widely discussed at international meetings and in excellent literature reviews.[9,10] As a result of this long and comprehensive developmental process, PI PLTs are being used in eight countries in Europe and work to gain experience using the technology is under way in four more. Approximately 80,000 units of PLTs PI using amotosalen have been transfused in Europe. Postmarketing studies of these PLTs as part of structured hemovigilance programs in Europe have not revealed unexpected problems or complications after approximately 20,000 units of amotosalen PI PLTs have been transfused to approximately 3,500 patients. The Phase III trials of amotosalen

fresh-frozen plasma (FFP) are completed; this product is approved in Europe and is now being used in two countries. Although PI of RBCs is technically more difficult and some methods were hampered by the development of antibodies in recipients, methods for PI of RBCs are under active study and may be available for implementation in coming years.

OTHER ISSUES CONSIDERED BY THE PANEL

Noninfectious hazards of transfusion

The panel recognized that the noninfectious hazards of transfusion such as TRALI and mistransfusion are more prevalent than currently recognized transmissible diseases and that PI does not address these problems. The panel did not believe that this issue should delay or inhibit the adoption of PI when the technology is ready. The panel urged that blood suppliers continue efforts to reduce these noninfectious complications but points out that the introduction of PI technology is not mutually exclusive of these efforts.

Rare risks

One concern with PI may be of a rare risk that would not be manifest until PI blood components have been transfused to a large number of patients. Although this problem may seem unique to PI, it really is not. Clinical trial data for licensure of any drug, biologic, or device will never be sufficiently extensive to identify very rare complications. The FDA must take rare risks into consideration with any drug, biologic, or device they license. Unfortunately, the United States does not have an effective system for postmarketing studies based on prelicensure data.[16] As the panel points out, this is the "weakest link in the regulatory process." They propose that licensure of PI mandate postmarketing studies as a condition of approval and that these studies might be somehow integrated with developing hemovigilance programs. An additional approach might include use of the RADAR project, which identifies previously unrecognized adverse drug and device reactions.[17] Follow-up of patients receiving amotosalen PI PLTs is linked with some hemovigilance programs in Europe.

Costs

The panel did not address the costs of implementing PI technology. They recommend that economic evaluations of PI should be carried out but emphasized that adoption of PI should be based on "considerations in addition to the results of an economic analysis."[1] Costs are "just one factor" in considering the use of PI. As the panel points out, many (most??) of the steps taken over the past two decades do not conform to the concepts of cost effectiveness used in other areas of medicine and health care. In the discussion of cost, the panel emphasized the importance of maintaining public confidence in the safety of the blood supply. This combined with the precautionary principle is consistent with other decisions regarding blood safety made over the past two decades and argues for the introduction of PI.

PI might not be as costly as some critics fear. In addition to elimination of the patient care costs of the diseases transmitted, transmission of agents not now tested should be prevented and those patients spared new infections. In the future, the countless hours spent in developing strategies to deal with new agents would be avoided and the costs of testing and loss of donors due to false-positive screening tests or medical history questions would be eliminated. In addition, irradiation of blood products, testing for bacterial contamination of PLTs, and testing for CMV and WNV could probably be eliminated; implementation of a test for trypanosomiasis could be avoided; and 7-day storage of PLTs could be reconsidered. Because plasma is replaced with a PLT additive solution during the amotosalen and potentially the riboflavin PI process, more plasma would become available for fractionation, thus providing some revenue. Because plasma is removed and because PI stops cytokine synthesis, transfusion reactions to PLTs should be decreased,[18] thus improving patient care and reducing the costs of managing these reactions.

Implications for developing countries

PI is discussed here in the context of developed countries. In many parts of the world, blood safety and transfusion-transmissible infections are a much greater problem than in developed countries. It is hoped that as PI becomes more widely used, the technology could be made available in some practical way in parts of the world where it is currently difficult to obtain an adequate supply of safe blood.

Implications of widespread adoption of PI

The panel also addresses several practical issues in the implementation of PI such as the problem of dual inventories. The amotosalen method for PI of plasma and PLTs widely used in Europe is different from that company's method under development for RBCs. Thus, that combination would not provide a single system for PI of all blood components. The riboflavin technology can be used for PLTs, plasma, and RBCs, making a single procedure effective for all components. Although currently there is no single licensed PI system for all blood components, the

panel felt that this should not delay adoption of PI for some components if overall considerations warrant its use.

If some, but not all, of the same blood component is subjected to PI, a dual inventory would arise. Both whole blood–derived (buffy coat) and apheresis PLTs are approved for use in Europe, so a single inventory of all PI PLTs is available there. It will be difficult to create a single inventory of PLTs in the United States, however, because whole blood–derived PLTs produced by the PLT-rich plasma method have not been studied in clinical trials. It seems unlikely that the United States would convert to buffy coat PLTs to adopt PI because only about 26 percent of PLTs in the United States are prepared from whole blood.[19] This problem could create pressure to speed the conversion to apheresis PLTs, motivate the manufacturers to develop a method for PI of PLTs produced with the PLT-rich plasma method, or provide incentive for the production of buffy coat–derived PLTs in the United States, (currently happening in Canada).

Patient selection issues

There is no evidence that components that have undergone PI pose a unique risk for any particular group of patients. The panel recommends that PI products be made available to all patients unless new data indicates an as yet unknown risk for specific patients. Thus, for instance, the panel concluded that there is no need to withhold PI components from neonates or pregnant women.

THE STAKEHOLDERS FOR OUR PI DELIBERATIONS

The panel recommends "broad public consultation" as part of the decision regarding adoption of PI. Stakeholders include industry, academia, the blood banking and/or transfusion medicine community including transfusion medicine physicians and leaders of blood supply organizations, physicians who use blood in their practice, regulators, and most of all patients.

Industry has done impressive work to develop PI technology and publicize their results. They have the responsibility to continue thorough, careful development of PI technology pursing appropriate safety and efficacy issues to produce a product that is helpful to patients and can be implemented into the blood supply system practically and realistically.

Academia also has a role. The companies developing PI technology do not have the breadth and depth of knowledge that exists in our universities. Thus, industry should avail themselves of this expertise and university scientists and physicians should collaborate when it is appropriate.

The blood banking and/or transfusion medicine community has the responsibility to consider PI with a view to the long-term future. Transfusion medicine physicians should have the patients' interest as their first priority. If PI improves transfusion therapy, which our European colleagues have concluded, then PI should be adopted more broadly. Leaders of blood supply organizations have the responsibility to consider PI with an open mind. The technology may be technically complex, but this issue should not deter us from being open to it. We have successfully implemented many complex technologies such as apheresis, radioimmunoassay, ELISA, and NAT. Thus, the consideration is whether it is time for a paradigm shift to further improve blood safety and, if so, whether PI is ready for adoption beyond Europe. PI may alter our current operations or be inconvenient, but these issues have been true of most improvements. Leaders of blood supply organizations have the responsibility to look beyond these short-term logistical issues.

Regulators play a key role in the evolution of PI. Their requirements must be consistent and based on scientifically sound and available data. It is essential that they speak with one voice and from a single point of view. It is reasonable to expect that they will look beyond the benefits of the elimination of existing transfusion-transmitted infections and take into account elimination of some current activities that may become redundant with PI introduction.

Physicians who use blood in their practice depend on those of us in the transfusion medicine and/or blood banking community to demonstrate leadership in providing high-quality transfusion therapy. Dialogue with and among these physician groups will be important to hear the concerns and questions of transfusing physicians, to educate them as to the benefits and unique aspects of PI products, and to determine the best ways to introduce PI blood components into clinical practice at the appropriate time.

Of course, the primary stakeholders are patients. They must be the focus of all of us in transfusion medicine and blood banking. It is our responsibility to provide adequate and safe transfusion therapy and to make available the appropriate blood products. To this end, we must ask the hard questions of the developers of PI, expect complete data and high-quality clinical trials, and be open to the introduction of technology that may be complex, challenging, or even disruptive to our present operations. If PI improves patient care, patients have a right to expect that we use our expertise and creativity to implement change.

CONCLUSIONS OF THE EDITORIALIST

The body of work to develop PI represents very substantial progress. PI is now widely used in Europe and has arrived at a point for realistic consideration in Canada and the

United States. I believe that the benefits of PI extend far beyond eliminating the small number of remaining infections from the traditional list of transfusion-transmitted infectious diseases such as hepatitis or HIV. The benefits include shortening the long list of other transfusion-transmitted infections that are not prevented by present technology or other methods of donor screening. The benefits will also be proven with emerging agents or changes in known agents such as SARS or Avian flu. In addition, irradiation of blood components could be eliminated, removing transfusion-associated GVHD as a lethal complication of transfusion. We are at the end of the usefulness of the present paradigm and must move to a new one. It is incumbent on all of us to consider PI in this broad context.

Jeffrey McCullough, MD
Department of Laboratory Medicine & Pathology
University of Minnesota
420 Delaware Street SE
Minneapolis, MN 55455
e-mail: mccul001@umn.edu

REFERENCES

1. Klein HG, Anderson D, Bernardi MJ, Cable R, Carey W, Hoch JS, Robitaille N, Sivilotti ML, Smaill F. Pathogen inactivation: making decisions about new technologies. Report of a consensus conference. Transfusion 2007;47: 2338-47.
2. Stramer SL. Current risks of transfusion-transmitted agents. Arch Pathol Lab Med 2007;131:702-7.
3. Peterson LR, Epstein JS. Problem solved? West Nile virus and transfusion safety. N Engl J Med 2005;353:516-7.
4. Pealer LN, Marfin AA, Petersen LR, Lanciotti RS, Page PL, Stramer SL, Stobierski MG, Signs K, Newman B, Kapoor H, Goodman JL, Chamberland ME. Transmission of West Nile virus through blood transfusion in the United States in 2002. N Engl J Med 2003;349:1236-45.
5. Charrel RN, Lamballerie X, Raoult D. Chikungunya outbreaks—the globalization of vectorborne diseases. N Engl J Med 2007;356:769-71.
6. Farnon E. Update: Chikungunya fever diagnosed among international travelers—United States, 2006. MMWR 2007; 56:276-7.
7. Nichols WG, Price TH, Gooley T, Corey L, Boeckh M. Transfusion-transmitted cytomegalovirus infection after receipt of leukoreduced blood products. Blood 2003;101: 4195-200.
8. Benjamin RJ, Wagner SJ. The residual risk of sepsis: modeling the effect of concentration on bacterial detection in two-bottle culture systems and an estimation of false-negative culture rates. Transfusion 2007;47:1381-9.
9. Bryant JB, Klein HG. Pathogen inactivation: the definitive safeguard for the blood supply. Arch Pathol Lab Med 2007; 131:719-33.
10. McCullough J. Pathogen inactivation: a new paradigm for preventing transfusion-transmitted infections. Am J Clin Pathol (in press).
11. Ciaravino V, McCullough T, Cimino G. The role of toxicology assessment in transfusion medicine. Transfusion 2003; 34;1481-92.
12. Corten L, Wieselhahn GP, Smyers JM, Murthy KK, McClure HM, Alter HJ. Photochemical inactivation of hepatitis B and hepatitis C viruses in human plasma as assessed in a chimpanzee infectivity model (abstract). Blood 2000;96: 60a.
13. Corash L, Lin L. Novel processes for inactivation of leukocytes to prevent transfusion-associated graft-versus-host disease. Bone Marrow Transplant 2004;33:1-7.
14. Fast LD, DiLeone G, Li J, Goodrich R. Functional inactivation of white blood cells by mirasol treatment. Transfusion 2006;46:642-8.
15. Osselaer JC, Doyen C. Routine use of platelet components prepared with photochemical treatment (INTERCEPT Platelets): impact on clinical outcomes and resources. Blood 2005;106:129a.
16. Psaty BM, Burke S. Institute of medicine on drug safety. N Engl J Med 2006;355:1753-9.
17. Bennett CL, Nebeker JR, Lyons E, Samore MH, Feldman MD, McKoy JM, Carson KR, Belknap SM, Trifilio SM, Schumock GT, Yarnold PR, Davidson CJ, Evens AM, Kuzel TM, Parada JP, Cournoyer D, West DP, Sartor O, Tallman MS, Raisch DW. The research on adverse drug events and reports (RADAR) project. JAMA 2005;293:2131-40.
18. McCullough J, Vesole DH, Benjamin RJ, Slichter SJ, Pineda A, Snyder E, Stadtmauer EA, Lopez-Plaza I, Coutre S, Strauss RG, Goodnough LT, Friday JL, Raife T, Cable R, Murphy S, Howard F, Davis K, Lin JS, Metzel P, Corash L, Koutsoukos A, Lin L, Buchholz DH, Conlan MG. Therapeutic efficacy and safety of platelets treated with a photochemical process for pathogen inactivation: the SPRINT Trial. Blood 2004;104:1534-41.
19. Sullivan MT, Cotton R, Read EJ, Wallace EL. Blood collection and transfusion in the United States in 2001. Transfusion 2007;47:385-94.

医薬品 研究報告 調査報告書

識別番号・報告回数			報告日	第一報入手日	新医薬品等の区分	機構処理欄
				2007. 12. 17	該当なし	

一般的名称	(製造承認書に記載なし)	研究報告の公表状況	Klein HG, Anderson D, Bernardi MJ, Cable R, Carey W, Hoch JS, Robitaille N, Sivilotti ML, Smaill F. Transfusion. 2007 Dec;47(12):2338-47.	公表国
販売名(企業名)	合成血「日赤」(日本赤十字社) 照射合成血「日赤」(日本赤十字社) 合成血-LR「日赤」(日本赤十字社) 照射合成血-LR「日赤」(日本赤十字社)			カナダ

研究報告の概要

○病原体不活化:新技術についての決断 コンセンサス会議報告
2007年3月29日～30日、カナダのトロントで、カナダ血液サービスとヘマ・ケベックが主催する病原体不活化(PI)に関するコンセンサス会議が開かれた。様々な分野の専門家9名で構成されたコンセンサス・パネルに対して提示された質問に回答する形で本報告はまとめられている。
近年の検査技術の発達により、現状の輸血感染症リスクは大変低く、PIを直ちに導入することは推奨しない。しかし、新興感染症のリスクは未知数であり、PIは予防手段として重要である。広範囲の病原体を不活化できる実現可能で安全な方法が確立されればPIを実施すべきである。
特に毒性の面では安全性と効果について厳格な基準を適用するべきである。各国の規制当局の間でデータを共有し、協力して取り組むことが望ましい。適切に計画された市販後調査も必要であり、副作用調査は全国的ヘモビジランスシステムと連携して行うべきである。
本格的な実施に先だって、安全性と効果に関するデータや採血・製造・保管など影響を受ける工程について、慎重に検討すべきである。患者や医師など関係者への十分な説明と、血液センターや病院などでの研修が必要である。最初は限定された地域でのパイロットプログラムとして導入すべきだろう。
不活化実施によって、現在行われている感染症検査など一部の安全対策を取りやめ、費用を削減できる可能性がある。
全ての血液製剤にPIを導入するためには、政府の支援と大規模な投資が必要である。

報告企業の意見	今後の対応
2007年3月29日～30日、カナダのトロントで行われた病原体不活化技術に関するコンセンサス会議の報告である。	日本赤十字社は8項目の安全対策の一環として不活化技術の導入について、各不活化技術の効果、血液成分への影響、製造作業への影響などの評価検討を行っている。細菌やウイルスを不活化する方策について今後も情報の収集に努める。

使用上の注意記載状況・その他参考事項等

合成血「日赤」
照射合成血「日赤」
合成血-LR「日赤」
照射合成血-LR「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク