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Alternative strategies in assuring blood safety: An Overview

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ABSTRACT

Assuring transfusion safety is an essential element of health care in all countries, requiring government commitment, national policy and a legal framework. Fundamental safety strategies include selection of low risk donors, Good Manufacturing Practices in preparation of blood components, and appropriate clinical use including avoidance of unnecessary transfusions. Hemovigilance, including surveillance for known adverse events and sentinel reporting of unexpected adverse events, enhances safety through benchmarking to promote best practices and by enabling rapid responses to new threats. Preventing transmission of infectious diseases is a principal safety concern. Selection of low risk donors includes use of screening questions to elicit risk factors known to be associated with transmissible infections. Laboratory testing for specific infectious disease markers is an established strategy for interdicting contaminated donations. The sensitivity, specificity, and operational convenience of laboratory testing have improved over time and newer technologies are imminent. Donor screening and laboratory testing, while highly effective in reducing risk, cannot eliminate all risk from known agents and must be developed de novo to address emerging infections. In contrast, pathogen reduction technologies offer the possibility for robust inactivation of a broad spectrum of blood transmissible agents and provide an added safeguard against newly emerging infectious threats of most types. Current pathogen reduction methods also inactivate leukocytes, adding safety benefits similar to leukocyte removal and product irradiation. However, to date, concerns about the safety and efficacy of cellular blood components treated by pathogen reduction have prevented approval of these technologies in the U.S. and Canada. FDA is promoting clinical and basic scientific studies to clarify these issues and would consider alternative approaches to assuring blood safety if pathogen reduction technologies are proven to be safe and effective.

1. Introduction

Newer technologies including gene based pathogen detection and pathogen reduction systems have expanded the possible approaches to assuring blood transfusion safety. However, each of the alternative strategies has benefits and limitations. The choice of a best approach therefore depends upon a clear understanding of these methods and how their characteristics will affect safety and cost in the setting of use. This paper discusses the relative merits of alternative strategies.

2. The transfusion safety paradigm

Safety of blood transfusion depends upon three fundamental elements: maximizing the safety, efficacy and availability of blood products, optimizing patient blood management, and hemovigilance.

2.1. Assuring safe and effective products

In any region, providing an adequate supply of safe and effective blood products for transfusion is a complex undertaking that requires a comprehensive system operating under regulatory oversight and quality management. The basic requirements of an effective blood system include government commitment and support, a national blood policy and plan, and a legal framework [1]. Within that system, organized recruitment of healthy low risk donors and laboratory testing for evidence of infectious diseases are the cornerstones of safe blood. Blood collection and processing need to follow documented Standard Operating Procedures consistent with current Good Manufacturing Practices. Standardization, documentation and quality control are needed in all areas including donor management, laboratory testing, aseptic collection and processing of components, labeling and tracking, cold chain, compatibility testing, reconciliation of unit assignment with a patient identifier, and bidirectional traceability (unit to patient and patient to unit). Adequate education, training and supervision of staff are essential. Ideally, the blood service should meet

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standards for external accreditation and the quality assurance program should include external audits.

Selection of healthy low risk donors is accomplished by use of donor deferral criteria. These criteria are based on medical, behavioral and geographical factors that are epidemiologically associated with transfusion transmissible diseases and are amenable to accurate history taking in the donor setting. This safety strategy reduces collection of infectious units that otherwise would enter the quarantine inventory and might be released due to false negative tests or by release error. Since donor deferral precedes any phlebotomy, the strategy also serves to protect blood center staff against possible infectious exposures. Additionally, donor deferral conserves resources by averting collection of units that must later be discarded as a result of positive laboratory tests.

2.2. Patient blood management

Transfusion carries risk even with the safest possible products. This observation leads to the concept of protecting patients by avoiding unnecessary transfusions. While simple in concept, this approach requires very sophisticated clinical management. Evidence-based "transfusion triggers" are difficult to define and vary with the clinical situation. Hence, optimal patient management lies in exercise of medical judgment with avoidance of transfusion as an automatic default. For example, some patients can be managed with colloid and crystalloid to correct hypovolemia when physiological tolerance of anemia is expected. Avoidance of transfusion also can be achieved by preventive recognition and treatment of conditions likely to result in a need for blood. Examples include pre-operative correction of anemia and coagulopathy. In the operative setting, blood loss can be minimized in a number of ways including blood sparing surgery, intra-operative and post-operative blood cell salvage and normovolemic hemodilution. Pre-operative autologous donation can reduce or avoid allogeneic blood exposures.

2.3. Hemovigilance

A third element of transfusion safety is hemovigilance, which consists of organized prospective monitoring and reporting of the outcome of transfusions (and other hemotherapies). Conceptually, hemovigilance can be divided into two activities, namely surveillance and sentinel monitoring. Surveillance is the comprehensive reporting of known adverse events and reactions under a framework of fixed definitions. Combined with denominator data on the overall number of transfusions, surveillance reporting permits the monitoring of trends and the detection of geographical and temporal clusters. These data permit recognition of system deficiencies, local benchmarking against best practices and meaningful assessment of the outcome of interventions. In contrast, sentinel monitoring is the detection and reporting of unexpected adverse events and reactions. Sentinel hemovigilance facilitates the identification of new threats and enables rapid system level responses. The use of standardized terminology, such as for case definitions, imputability and severity, improves data quality and allows data from different sources to be aggregated or compared. Although it is not operationally a part of blood collection and use, hemovigilance plays a critical role in the assessment and progressive improvement of the blood system. For this reason, it needs to be regarded as an essential function.

3. Effectiveness of the conventional blood safety strategy

Donor selection, laboratory testing for infectious diseases and aseptic processing and storage constitute the conventional approach to maximizing blood product safety. In the U.S. and other countries, these methods, which include nucleic acid testing for HIV and HCV, have lowered the major risks from viral infections to levels that cannot be measured directly. In the U.S., current risks have been estimated at 1 in 1.5–1.8 million per unit for HIV and HCV, and 1 in 174,000–269,000 for HBV [2]. In contrast, the risk of bacterial contamination of platelets is less well controlled. The American National Red Cross reported for the period of 2004–2006 that the rate of clinical sepsis ranged between 1:41,000 and 1:193,000 with a fatality rate of approximately 1:500,000 despite interventions including screening with bacterial cultures [3].

3.1. Value of donor questioning

Donor selection by the use of questionnaires is intended both to protect the health of the donor and to lower the risk of collecting an infectious unit. Deferral of candidate donors based on risk factors for transmissible infections prevents the collection of contaminated units that might otherwise be released from inventory through error. Additionally, risk factor screening compliments laboratory testing by avoiding collections in the "window period" of recent infection when laboratory tests may be negative and serve as an added precaution against procedural failures that can result in falsely negative tests. In urgent situations, where testing and/or pathogen reduction are infeasible, donor selection criteria may be the only safeguard. The same is true for controlling the risk of variant Creutzfeldt–Jakob disease since no screening tests currently exist. Donor selection criteria sometimes have surrogate value. For example, for donors in a non-endemic area, deferral based on a history of malaria exposure in an endemic area might prevent transfusion risk from an emerging disease in the malaria endemic area.

Compared with laboratory testing, donor screening by the use of questionnaires suffers serious limitations of sensitivity and specificity. Low specificity is especially problematic because it can result in a significant loss of healthy donors and can undermine public confidence in the blood system. Also, validation of donor questions is often lacking. Few validation studies of donor questions have been done mainly due to the difficulty in performing adequately powered studies in deferred donors. Recently, investigators at the American National Red Cross demonstrated a strong correlation of admitted risk factors for hepatitis with markers of hepatitis infection in deferred donors. However, they were unable to demonstrate a comparable association of infectious disease markers with donor responses to other risk questions. It is unresolved whether the absence of a demonstrated association was due to lack of value of the other questions or due to the limited study size [4]. This problem is aggravated by the fact that donor questions often are introduced without objective validation. While empirical use of donor questions may be a prudent response to an emerging threat, their use can remain unexamined scientifically even after effective testing is introduced.

3.2. Value of donor testing

Laboratory testing for markers of infectious diseases has profoundly improved blood safety in recent decades. Donor testing can be highly cost-effective, though this depends on the prevalence of infections in donors, the performance characteristics of the tests and their costs. Additionally, testing contributes to individual and public health through the notification of infections in donors, permitting donor education, treatment and the exercise of preventive measures against secondary spread. Also, when linked to demographics, marker rate data obtained through testing provide epidemiological information that can be used to identify

the sources of risk as well as the safest donors. Such information can be used in routine public health surveillance, such as for prevalence of syphilis and HIV in the population, and at times to monitor epidemics, as has been the case in the U.S. outbreak of West Nile Virus.

A comparison of marker rates for transfusion transmitted infections in the general population with rates in first time and repeat donors provides an estimate of the effectiveness of donor deferral criteria and laboratory testing. Representative data available in the U.S. are shown in Table 1. It can be seen that first time donors have on average a marker prevalence that is 75–97% lower than that in the general population, confirming the effectiveness of donor deferrals based on risk factors. A further reduction of marker rates of about 10 to 50-fold comparing repeat donors to first time donors demonstrates the value of testing. As infected persons are barred from future donations, the prevalence of infections in repeat donors is markedly reduced. Incidence of new infections in repeat donors may or may not be lower than in first time donors, though lower incidence is likely due to the fact that repeat donors are persons already selected through prior questioning for the absence of risk factors.

4. Advancements in donor testing technology

Major advancements have taken place recently in the technologies that assure blood product safety. In particular, innovations in laboratory testing for infectious disease agents using nanoparticle-based assays may permit more rapid and less operationally complex testing compared with nucleic acid amplification, but with comparable sensitivity and specificity. Also, test methods using microarrays now permit a broader range for concurrent detection of multiple agents of concern than is possible with conventional immunoassays or nucleic acid amplification. A review of these newer technologies is beyond the scope of this paper. However, a few examples may serve to illustrate the potential of some of these methods.

4.1. Nanoparticle and microarray-based assays

Particles in the size range of 100 nm or less, called nanoparticles, can now be engineered to contain ligand-specific binding sites and a variety of mechanisms for capture, sorting and differential signal readout [9]. They can be designed for antibody, antigen or gene sequence detection. Nanoparticle-based assays generally are rapid, exhibiting liquid phase rather than solid/liquid phase type kinetics for comparable chemical interactions. Also, it is possible to mix nanoparticles with diverse detection specificities, each of which exhibits a different readout signal such as light emission at a distinct wavelength, to obtain concurrent detection of multiple analytes in a single "multiplex" assay. Because of the enormous surface area achieved with very small particles, and the added potential for signal amplification by a variety of techniques, assays based on nanoparticles can achieve sensitivities on the order of 100-fold greater than ELISA, often comparable to nucleic acid amplification methods.

Microarrays are assays in which multiple ligands are displayed as an array on a solid phase such as a glass slide, which is later incubated with a test sample [10]. They can be designed for antibody, antigen or nucleic acid detection. For example, microarray assays for gene sequence detection involve printing of "capture" gene sequences at predetermined positions on the solid phase. Exposure to a test sample of nucleic acids results in the simultaneous annealing of "target" gene sequences to the capture sequences on the solid phase. Labeled "detector" sequences can then provide both signal amplification as well as readout. Identification of the detected target gene sequences is obtained by noting the position of the positive signals on the pre-structured array.

Although microarrays do not have the advantages of liquid kinetics and the requirement for a solid phase presently prevents high throughput designs, they have the potential for simultaneous detection of thousands of analytes. In theory, this property should permit concurrent screening and confirmation of essentially all known transfusion transmitted pathogens by a single test on a blood sample. However, the optimal conditions for amplification and binding of different target sequences may differ enough to limit the "multiplex" capacity of a single microarray assay.

Microarray and nanoparticle methods can be combined in the same system, providing a "multiplex" assay that is both highly sensitive and specific. An example is shown in Fig. 1. In this "proof of concept" experiment, the limit of detection of a genomic microarray assay (each spot specific for a different viral gene fragment) was 150 copies of purified West Nile Virus RNA. In comparison, the sensitivity of an in-house RT-PCR assay was 30 copies.

4.2. Aptamer technology

Aptamers are small self-folded sequences of nucleic acids that can be generated by combinatorial methods and then selected for extremely high affinity to bind to a given ligand [11]. Selected aptamers with high affinity for target regions of a pathogen can be used to capture and isolate the pathogen, e.g. by use of aptamer coated magnetic beads. The protein antigens or nucleic acids, which have been concentrated by affinity to the aptamers, can be subjected to a direct detection assay. Captured nucleic acid targets can be further amplified, such as by use of PCR on eluted DNA. Aptamer technology may be of particular value to enhance the sensitivity for direct detection of parasites in donor blood samples. In an asymptomatic donor, the level of parasitemia is often so low that the chance to obtain a parasite in a test sample of practical size for an antigen or nucleic acid assay precludes the use of an otherwise sensitive assay. Concentration of a large volume test sample with high affinity aptamers might overcome this limitation. Aptamers also can be bound to filters to remove pathogens by filtration of a unit of blood. This technology may be especially useful for removal of prions since detection assays are not available.

5. Pathogen reduction technologies

Pathogen reduction technologies are methods that expose whole blood or separated blood components to chemicals, often in combination with UV light, that interact with nucleic acids to result in irreversible strand breakage and/or strand linkage [12]. The specific technologies are not described in this paper. In principle, since red blood cells, platelets, and obviously plasma do not require intact nucleic acids to function as transfusion products, the effect of these exposures is selective inactivation of pathogens with conservation of the blood product. However, some damage to cells and proteins can occur. Leukocytes in the blood product usually are inactivated, but this can be beneficial in reducing leukocyte related toxicities of transfusion including febrile nonhemolytic reactions, alloimmunization and graft versus host disease [13].

Table 1
Laboratory markers for transfusion transmitted diseases (percent positive) in U.S. blood donors compared with the general U.S. population.

	General population	First time donors	Repeat donors
Anti-HIV	0.36 [7]	0.011 [5]	0.001 [5]
HBsAg	0.3–0.5 [6]	0.074 [5]	0.002 [5]
Anti-HCV	1.6 [8]	0.287 [5]	0.006 [5]

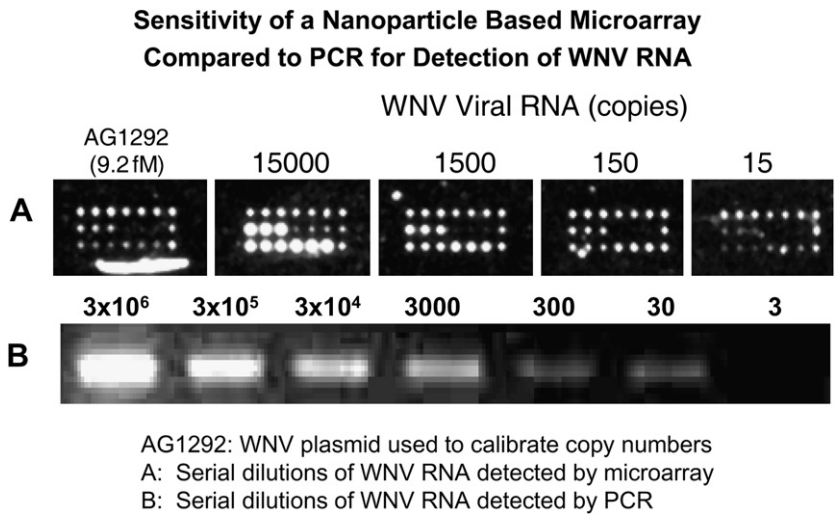

Fig. 1. Relative sensitivity of a prototype nanoparticle based microassay for WNV was compared with RT-PCR by serial dilutions of purified WNV genomic RNA. End-point detection by nanoparticle microarray was 150 copies (A), compared with end-point detection by RT-PCR of 30 copies (B). Copy numbers of WNV genomic RNA were determined by comparison against a reference WNV plasmid (AG1292).

Methods of pathogen reduction for individual and for pooled plasma components have been in widespread use in many countries for more than a decade. Safety of these products has been excellent in general, however, one product (a solvent/detergent treated pooled plasma) marketed in the U.S. was associated with serious thrombotic events in the setting of liver transplantation and is no longer manufactured [14]. Two pathogen reduction methods for platelets are CE marked in Europe and implemented in some countries, but still are considered investigational in others [12]. As yet, no method has been validated as safe and effective for pathogen reduction of either whole blood or red blood cell concentrates, though scientific progress is being made in these areas.

5.1. Advantages of pathogen reduction over donor questioning and testing

Pathogen reduction offers many potential advantages over donor questioning and testing as a blood product safety strategy. Donor questioning and testing, while highly effective to prevent many transfusion transmitted infections, have limitations of sensitivity resulting in a residual risk, albeit sometimes very small. In contrast, for most agents, pathogen reduction is more highly robust, leaving little if any risk. Pathogen reduction methods additionally are effective in killing bacteria, which are not as readily detected or removed by any other current strategy. This may permit extension of the storage life of platelets, which is limited in part by the possibility of bacterial contamination with growth at room temperature. Questioning and testing also are "after the fact" interventions that depend on prior recognition of infectious threats. Often it takes years to develop suitable questions and donor testing methods to address known and emerging threats, during which time blood recipients remain at risk. Pathogen reduction is thus a precautionary strategy, for which reason some have regarded it as a new safety paradigm [15].

To the extent that donor questioning and testing might be reduced with implementation of pathogen reduction, there may be further benefits to adequacy of the blood supply. Inactivating pathogens in the product does not cause any unnecessary donor loss, unlike questioning and testing which have inherent limitations of specificity. Donor questioning also takes time, possibly affecting some willingness to donate. While donor notification of true positive test results has health value, deferral of donors based on falsely positive tests generates personal anxiety and contributes to otherwise unnecessary medical costs from further evaluations. Fear of a false positive result also can discourage some donors. Elimination of testing, should it be feasible, also would eliminate test seeking as a motivation for donation by persons with self-identified risk factors for transmissible infections.

5.2. Limitations of pathogen reduction

An ideal pathogen reduction system would eliminate all risk of transfusion transmitted diseases at an affordable cost without causing harm to patients, product handlers or the environment. While the profile of the available technologies is highly favorable in most respects, there are some limitations and uncertainties.

5.2.1. Efficacy limitations

The methods in current use and development have shown a remarkable capacity to inactivate a very broad range of viruses, parasites and bacteria, including intracellular agents in red blood cells and leukocytes. However, the demonstration of pathogen killing is limited to the titer of the "spike" that is used experimentally to challenge the product and the sensitivity of the assay system used to detect residual infectivity after treatment of the product. For some viral agents, the demonstrated level of pathogen reduction is close to or below the titer that can be present in the blood of an asymptomatically infected donor. This is the case for HIV, HCV and HBV. For this reason, it would be prudent for blood systems to retain laboratory tests for these agents. The effect of testing would be to allow use only of donations with viral loads below the level of detection of the laboratory assays. Any otherwise acceptable infectious units would then have only low levels of virus, assuring that the pathogen reduction process would have an inactivation capacity greatly in excess of the viral burden. The difference in inactivation capacity and viral burden defines a safety margin for the pathogen reduction process. Precedents for pathogen reduction in plasma derivatives suggest that a margin of safety of at least $3\log_{10}$ is desirable for safety assurance. Consideration also needs to be given to the kinetics of pathogen reduction, which can vary both by the method and the disease agent. Slower kinetics may imply less robust clearance. Additional limitations include the general resistance of bacterial spores to pathogen reduction methods and the inability of the available technologies to inactivate infectivity associated with prions.

5.2.2. Safety issues

While the direct toxicity of the chemicals presently used in pathogen reduction has been close to nil, damage to some transfusion products has been observed, raising questions about the overall clinical risks and benefits of treated products. Some efforts at pathogen reduction for red blood cells have been abandoned due to the development of neoantigens that induced antibodies, although without clinical evidence of hemolysis [16]. Platelet recovery and survival have been reduced compared with untreated products [17]. While adjustment of platelet dosing can offset these effects in terms of platelet delivery, these observations raise the issue whether potential damage to platelets has clinical significance. In particular, the FDA has been concerned about the findings in one Phase 3 study in the U.S. of an increase in adverse events and serious adverse events compared with controls when psoralen/UV treated platelets were given to thrombocytopenic patients [18]. All of the statistically significant adverse events in that study were seen in the treatment group. The reported findings of an excess in lung injury (pneumonitis and ARDS), though not definitively established as product toxicities, are especially worrisome in consideration of their potential clinical significance. The adverse findings of this study stand in contrast to the absence of serious adverse events reported through hemovigilance systems in countries that have implemented pathogen reduction of platelets by this method. Nevertheless, it is FDA's position that clinical safety of platelets treated by this method needs to be confirmed in a prospective study designed specifically to address the previously observed adverse events.

5.3. Reexamination of the blood safety paradigm

Adoption of pathogen reduction technologies, when available for all transfusion components, will create an opportunity to reexamine the conventional product safety paradigm. The impact of policy changes in this area will need to be evaluated carefully to avoid unintended consequences. For example, pathogen reduced blood components might be associated with risks unrelated to blood borne infections. Specifically focused hemovigilance reporting may be needed to detect such effects. While it may remain important to screen and test donors for high titer infectious agents including HIV, HCV and HBV, consideration could be given to removal of donor deferral criteria and laboratory tests that are directed at pathogens which are present only at low levels in the blood and for which pathogen reduction methods have been demonstrated to provide a large margin of safety. Examples might include West Nile virus and parasitic agents. Additionally, pathogen reduction might replace laboratory testing and leukocyte removal for control of leukocyte associated infections such as CMV and HTLV, and may obviate the need for gamma irradiation to prevent graft versus host disease.

6. Summary and conclusions

Conventional approaches to assuring blood product safety through donor questioning and laboratory testing have been highly effective for controlling risks from the major blood transmissible diseases. Additionally, newer technologies in laboratory testing including nanoparticle-based assays and microarrays offer potential advancements in sensitivity, specificity and operational efficiency (e.g. more rapid and "multiplex" testing). In particular, nanoparticle-based methods can approach the sensitivity of gene amplification tests, but in much simpler systems. Use of aptamers to bind ligands with high affinity may further enhance assay sensitivity and could lead to a new generation of pathogen binding filters. Despite their overall effectiveness, donor questioning and laboratory testing are not well adapted to addressing emerging infectious threats since they are reactive strategies that depend on development of specific new interventions.

In contrast, pathogen reduction technologies, which are well established as cornerstones of safety in the manufacture of plasma derivatives, offer a prospective safeguard against emerging infections that could affect blood safety. Technologies for pathogen reduction in plasma components are in wide use, and similar methods to treat platelet products have been introduced in some countries. Pathogen reduction methods for whole blood and red cell concentrates have faced technical obstacles, but are under active development. Current pathogen reduction technologies have a broad range of effectiveness against viruses, parasites and bacteria. In particular, they offer improvements over current methods for control of bacterial contamination in platelets. Additionally, their use could supplant leukocyte removal and gamma irradiation for control of leukocyte associated toxicities. With the exception of one solvent/detergent treated plasma product, concerns about the safety and efficacy of blood components treated to reduce pathogens has prevented their regulatory approval in the U.S., however, FDA encourages further studies in this area. Opportunities to advance the field through further research recently were discussed at an NIH sponsored workshop [19].

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