Pathogen Inactivation of Cellular Blood Products – More Security for the Patient or Less?

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Numerous measures have been introduced to prevent infection of patients during transfusion of blood components and plasma derivatives. These efforts have drastically reduced the residual risk of classical transfusion-related infections by hepatitis B (HBV) and C (HCV) and human immunodeficiency virus (HIV). In addition to excluding donor risk groups, these measures include continuously improved serological diagnosis and, in recent years, molecular biological diagnosis. In the meantime, the residual risks for infection with these agents have become exceedingly small. In Germany, the number of blood product-transmitted HIV infections reported to the Paul Ehrlich Institute (PEI) amounted to less than 1 infection per year (residual risk < 1:5,000,000) [1]. A further reduction can be expected with the obligatory introduction of HIV-PCR [2]. Since the general implementation of HCV-PCR, not a single transfusion-related infection has been reported [1]. Seifried et al. [2] reported a residual risk of 1:13,000,000 [2].

As a result of these successful efforts some pathogens that received less attention in the past are now coming to the fore: In particular thrombocyte concentrates offer, as a result of their storage temperature, excellent conditions for bacterial growth. According to data in the literature, 1 out of 2,000 concentrates is reported to be contaminated with bacteria [3], and according to Montag et al. [4], 1 out of 3,000–5,000 single-donor concentrates, with 1 out of 50,000 thrombocyte transfusions leading to sepsis in the recipient. Incidents resulting from transfusion of erythrocyte concentrates are less frequent but, due to nature of the pathogens, are generally more serious. Data from France showed that 1 out of 600,000 recipients of cellular blood products died as a result of the presence of bacteria in the transfused blood product [4]. In Germany this would correspond to 8 deaths per year. Figures obtained by the PEI, however, are considerably lower [1]. It is unclear so far if some of these infections were not recognized as transfusion related, if they were not reported, if the French figures are an overestimation or if there is a significant regional difference [3] in the frequency of these incidents. The number of incidents are ex-

pected to clearly drop as a result of the introduction of predonation sampling.

Until the beginning of the 1980s, almost all recipients of coagulation factor concentrates became infected with HBV and/or HCV because the single risks of each plasma sample were multiplied by pooling. Consequently, procedures were developed to achieve inactivation of these pathogens in the preparations, but these only came into general use as a result of the HIV epidemic. However, with the first generation of pathogen-inactivated blood products a number of infection events still occurred [surveyed in 5]. Model experiments led to improved validation of security for the individual treatment steps. Today, virus inactivation of plasma derivatives provides a very high degree of safety.

To some extent fresh plasma has also been subjected to pathogen inactivation. The increased level of safety is purchased at the price of a reduction of the activity of some coagulation factors and inhibitors, the clinical relevance of which is controversially discussed. A 4-month quarantine is an alternative to pathogen inactivation of fresh frozen plasma and leads to a similar level of safety for those pathogens that have been tested.

Quarantine storage of cellular blood products is hardly possible. In view of the fact that the public senses transfusion-related infections, in spite of their very small number, as a threat, and with respect to the repeated appearance of new pathogenic agents which in the first instance cannot reliably be detected or the transmission of which cannot be ruled out by the exclusion of risk groups, the question arises whether or not the introduction of pathogen inactivation of cellular blood products would be reasonable and increase the safety of blood component transfusion.

Pathogen inactivation techniques for cellular blood products have not yet been approved even though some of them are presently undergoing clinical testing.

Basically, three aspects of the evaluation of methods for pathogen inactivation are matter of debate:

– *The effectiveness of the method.*

The effectiveness is examined by model experiments. In such model experiments impressive evidence has been obtained for the effectiveness of inactivation of numerous pathogens. For other infectious agents, it is difficult to introduce similar high-titer virus loads as those occurring in vivo, and/or the proof of inactivation is difficult. It can be considered certain that the inactivation methods used cannot effectively inactivate any concentrations of all possible pathogens so that donor selection and testing cannot be abandoned.

– *The effects of the method on the (concurrently) treated blood cells.*

Possible consequences of pathogen inactivation are reduced function of the treated blood cells, resulting in insufficient hemostasis as well as an increased demand for thrombocytes and a potential neoantigenicity, i.e. a surface alteration giving rise to an increased elimination of the cells from circulation.

– *Possible mutagenic and carcinogenic effects of the pathogen-inactivated preparation on the recipient.*

The substances used for inactivation function by interacting with the nucleic acids of the pathogen. They are to a large extent, but not completely, removed from the preparation. According to current knowledge, there is no threshold level below which the mutagenic and/or carcinogenic effects of such substances completely disappear. Animal experiments, however, did not show any indication of a mutagenic and/or carcinogenic effect related to the inactivation procedures. Thus, the question arises as to the degree of certainty with which such a nonobservation rules out the occurrence of the non-observed events. This question is of relevance because the number of persons potentially injured as a result of pathogen inactivation (death by cancer, injury as a result of functionally insufficient preparations) should not exceed the number of persons injured by infections resulting from noninactivation.

Due to the extremely low incidence of serious injuries as a result of infections arising from blood products, it is very difficult to demonstrate on balance that pathogen inactivation at the very least does not represent a disadvantage for the patients. However, a quantitative estimate of the risks connected with this new technology is essential *before* the method is widely introduced. Widespread clinical use may result in damage orders of magnitude greater

than its usefulness while possibly evading statistical analysis as a result of the background incidence of malignant diseases in the population.

This conservative assessment may change if a new pathogen appears that cannot be controlled by donor selection and laboratory testing and that leads to a high rate of morbidity and mortality in transfusion recipients. SARS did not become a problem for blood donations. In contrast, transmission of West Nile Virus (WNV) did occur in the endemic area of North America in the year 2002 [6]. Not until 2003, transmission of this type was widely, but not completely, avoided by NAT of WNV.

The efficacy of at least one method of pathogen inactivation has been demonstrated in relationship to WNV. However, the blood donation facilities that were affected presently do not plan to introduce pathogen inactivation of cellular blood products.

The considerations mentioned above did not take into account the increased costs of the new preparations since discussion of the commensurability of costs and benefits is only expedient if the net benefit of the preparations for the patients can be convincingly demonstrated.

The 'Expert Committee on Blood Transfusion' of the Council of Europe commissioned a study on pathogen inactivation of blood components for 1999–2000. The results of this study, which comprise material worth reading, were published in a Council of Europe document and in *Transfusion Medicine* [7]. Thereupon the Committee of Ministers of the Council of Europe recently published recommendations for its member nations [8]. In the following, the key sentences of these recommendations are given.

The Council of Europe 'recommends to governments of member states to take account of the following considerations regarding the introduction of pathogen inactivation procedures for blood components, if necessary by the relevant competent authorities:

1. current safety standards of blood components are high;
2. incremental costs of pathogen inactivation procedures are high in relation to the additional safety gained;
3. the cost effectiveness of pathogen inactivation methods and the evidence of health gain for the individual have not been established;
4. pathogen inactivation methods may have a negative impact on the efficacy of blood components and may harbour unexpected long-term adverse effects.'

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