Plasma pool size and the safety of plasma derivatives

For several decades, various preparations of coagulation factors VIII and IX have played an invaluable role in the treatment of the hemophilias. As their availability increased, the effectiveness and convenience of freeze-dried concentrates of these factors made them the treatment of choice for many patients, notwithstanding the associated high risk of hepatitis. At the time of the recognition of the human immunodeficiency virus transmission risk associated with these products, measures for virus inactivation directed at hepatitis viruses were beginning to show promise.

The detection and removal of virus-contaminated donor plasma and virus inactivation of the final products have vastly increased product safety in recent years.[1] The possibility that new agents contaminating these products will emerge and the resistance of certain known viruses to current inactivation methods justify not only intensive surveillance, but also continuing efforts to develop and apply new solutions to the problem of viral contamination of plasma pools. To this end, a variety of approaches have been tried or recommended over the years.[2]

One suggested approach for reducing the risk of pathogen transmission by pooled plasma derivatives is the use of smaller pools to lower the likelihood that a contaminating unit will find its way into an individual pool. In this issue of **TRANSFUSION**, Lynch et al.[3] report on reductions in the number of donor units entered into plasma pools and the effect of those reductions on the risk of exposure to contaminating microbes in the recipients of such units. Their study is exemplary of the kind of analysis needed in considering this and other measures for increasing the safety of blood and blood products. These authors show that, except in the case of extremely rare pathogens, a reduction in pool size is not a very promising approach to increasing the safety of pooled plasma products in persons who require frequent treatment over many years, such as persons with moderate or severe clotting factor deficiencies. Very similar conclusions were reached by an earlier group commenting on the small-pool strategy, but with less thorough mathematical modeling.[4]

Lynch et al. demonstrate that large pools are highly likely to be contaminated and that large reductions in pool size are necessary to lower this likelihood, unless the prevalence of the agent in the donor population is extremely low. Furthermore, when an individual's lifetime treatment requires as many as 100 lots of a pooled plasma derivative, the likelihood of exposure to a contaminating agent is 63 percent when only one of the pools is contaminated. Their model supports the conclusion that reducing pool size does not compare favorably with other measures currently in place that screen out units from infected donors by a variety of donor screening and laboratory tests and by inactivation of contaminating viruses during production. The empiric evidence is overwhelming in support of the value of virus inactivation, which is currently most efficient for the lipid-coated viruses: human immunodeficiency virus and hepatitis B and C viruses. At this time, inactivation or removal methods for viruses lacking a lipid coat (hepatitis A virus and parvovirus B19) and for more resistant agents, such as the putative causative agent for Creutzfeldt-Jakob disease, have not been developed to a satisfactory state. Although the case for testing donor plasma for the known blood-borne pathogens is inherently logical, it rests heavily on evidence from single-donor products, more so than on evidence from pooled plasma derivatives.

Certain circumstances are alluded to by Lynch et al. in which attention to pool sizes and sources could confer some benefit, at least temporarily. For example, if a newly emerging agent is uneven in its geographic distribution, as is likely to be the case at the beginning of an epidemic, products made from local donations in sites where the agent has not yet emerged would have greater safety that would large pools made from a variety of collection regions, including those where the agent is emerging first. The relative advantage of this approach would naturally decline as the prevalence of the agent becomes more uniform and widespread; this is the posited condition for the analysis of Lynch et al.

What other options are there, then, beyond state-of-the-art donor screening, laboratory tests, and virus-inactivation and -removal technologies? One solution at hand for some plasma proteins is to make synthetic proteins, using recombinant DNA technology. As with all therapeutic interventions, there are already known and hypothetical scientific, logistic, and practical disadvantages of this approach, but it does have the virtue of eliminating the problem of transmitting blood-borne pathogens from donors, which has haunted the remarkable therapeutic success seen with coagulation factor replacement therapy up to this time. Farther out on the horizon is the prospect for the in vivo correction of protein deficiencies via gene therapy, with the enormous potential advantage of a prolonged benefit obviating the requirement for replacement therapy over many years, as well as eliminating the transmission of blood-borne pathogens.

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