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Pathogen Reduction Technology in Transfusion: Where Do We Stand?

Mohammad Khurshid¹ and Bushra Moiz²

Blood transfusion is a lifesaving intervention, having a central role in patients' management. However, it is not free of risks. One of the major challenges is Transfusion Transmitted Infections (TTIs) by viruses, bacteria and protozoa which are determined by their presence in the donated blood and their survival during blood storage. Important among these infections are viral hepatitis B, C, Human Immunodeficiency Virus (HIV), and syphilis. WHO recommends an additional screening for malaria, Human T Lymphocyte Virus (HTLV) and Chagas disease for some countries as per epidemiology. Dengue, hepatitis E, Parvovirus, Chikungunya and West Nile Viral (WNV) infection constitute new emerging viruses. Pathogens like Cretuzfeldt-Jacob variant disease organism and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) are the dreaded ones though there never has been an evidence of their transmission through transfusion.¹ Moreover, because of distinctive storage temperature requirements (20 - 24°C) for platelets units, bacterial contamination remains a potential threat for these blood products.

Strategies like donor interview, testing for disease markers, appropriate storing, leuco-depletion have significantly reduced the risk of TTIs. Besides, evidence-based transfusion guidelines, directed towards judicious usage of blood components, minimize the exposure of patients to potentially infectious blood or blood products. Recent technology like Nucleic Acid Testing (NAT) reduces the risk of window period donations for Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), and Hepatitis C Virus (HCV). Encouraging reports on utilizing NAT have emerged from Southern² and Northern Pakistan.³ A recent meta-analysis showed that weighted average for sero-prevalence is 2.3% for HBV and 2.8% for HCV in our blood donors⁴ while risk of window period donations is 1:13900, 1:10900 and 1:62600 respectively for Hepatitis C Virus (HCV), Hepatitis B Virus (HBV) and Human Immunodeficiency Virus (HIV).²

To eliminate window period donations and to guard against new and ever-increasing infectious agents, tools for pathogen inactivation have been established. One of the most initial strategies in 1977 was heating of albumin for preventing the transmission of hepatitis. Germany was the pioneer for using heating to inactivate pathogens in coagulation factor concentrates though at the cost of reducing efficacy of clotting factors. Recognition of Acquired Immuno Deficiency Syndrome (AIDS) in 1985 in a hemophilia patient, provoked the initiation of some virus inactivation procedures in factor-VIII and factor-IX concentrates.

To address the issue, Solvent Detergent (SD) and Methylene Blue (MB) / visible light were the initial Pathogen Reduction Technologies (PRT). These were used for removing viruses and parasites in plasma only, as both were detrimental to cell membranes. SD, followed by filtration method, inactivates lipid enveloped viruses, protozoa and prions. However, SD treatment is less effective in eliminating non-enveloped viruses like hepatitis A and parvovirus B.⁵ Moreover, SD treated plasma may lower clotting factors (factor V, VIII, vWF) and ADAMTS-13 and protein S.⁶ MB gets incorporated in the viral nucleic acid and produces free oxygen radicals on exposure to visible light inhibiting viral replication. MB is effective in eliminating enveloped viruses as well as some non-enveloped viruses, but cannot permeate bacterial and white cell walls.⁷ Therefore, it is ineffective in reducing bacteria or preventing transfusion associated graft-versus-host disease. Since MB remains localized to external surfaces, it can be used as a pathogen reducing agent for plasma only and not for cellular products.⁵ Latest technologies use photosensitizers like amotosolen and riboflavin with Ultraviolet (UV) rays to treat cellular products, e.g. platelet concentrates.⁵ Both the agents intercalate with nucleic acids of pathogens and upon UV light exposure interfere with replication by either cross-linking (amotosolen) or oxygen independent electron transfer (riboflavin). Non-enveloped viruses such as hepatitis A or E are resistant to inactivation by amotosolen.⁷ Moreover, amotosolen treated plasma should not be used for neonates receiving phototherapy for hyperbilirubinemia as it can produce erythema.⁷ These are effective in removing enveloped viruses, bacteria, protozoa and white cells from plasma and platelet units. Amotosolen can prevent graft versus host disease and transfusion transmitted cytomegaloviral infection. Another rapidly evolving technology is using ultraviolet

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(UV) C without photosensitizers to interrupt synthesis of nucleic acids by pathogens. It is a simple method using UVC (245 nm) which effectively removes virus, bacteria and parasite and does not require filtration of photosensitive products. However, because of its short wave length, it cannot penetrate turbid or protein containing solutions. Therefore, UVC can be used to reduce pathogens in apheresis or buffy coat platelets containing additive solution.⁷ Though PRT is routinely used in many European countries to treat plasma and platelets, but currently it is not available for red cells concentrates. However, clinical trials have reached such a level where the technology will be utilized for red cells as well.⁵

So where do we currently stand in terms of safety and efficacy of PRT? Previous strategies for maximizing safety of blood resulted in donor deferral and reduced blood supply. Pathogen reduction is an attractive option to remove/inactivate residual known and unknown bacteria, viruses and protozoa. PRT was successfully used for removing bacteria, Hepatitis A Virus (HAV), parvovirus, Chikunguniya from blood products. Moreover, PRT interrupts cell membranes of leucocytes in donated blood with subsequent additional benefits of preventing Cytomegalovirus (CMV) infection, febrile reactions, platelet refractoriness and transfusion associated host disease which has a high mortality rate.⁵ One of the major apprehensions for implementing PRT was the toxicity of chemicals used. Extensive pre-clinical toxicology for MB, amotosolen and riboflavin showed that the toxicity risk for carcinogenesis, mutagenesis and reproductive health is minimal as small quantities of chemicals used.⁸ Moreover, UVC based technology is devoid of photoactive substances and, therefore, does not induce harmful effects related to photoactive substances.⁹ Similarly, solvent and detergent levels are too small in SD plasma to impose health hazards. What is the clinical utility of pathogen reduced blood products? Six randomized clinical trials (RCTs, five based on amotosolen and one on riboflavin), have been conducted to determine the platelet increment in pathogen reduced platelet transfusions in oncology patients.⁵ These trials showed lower platelet increment and increased frequency of platelet transfusions, with treated compared to non-treated platelets. Similarly, two RCTs studied pathogen reduced plasma (using amotosolen and MB/SD) in hepatic coagulopathy.⁵ They concluded that efficiency of treated vs. untreated plasma was same; however, patients receiving MB treated plasma required 14% more plasma infusion. More RCTs are needed to evaluate the differences in clinical outcomes in terms of bleeding and adverse effects of pathogen reduced blood products. As per current recommendations, PRT is used as an addition rather than replacement for preventive strategies. Hence, PRT will add to the existing cost of blood products. Most

comprehensive cost benefit analysis was done by Custer *et al.* in Canada.¹⁰ They reported a cost of \$44.0/donation for their current screening for HIV, HBV, HCV, WNV, HTLV1/2 and syphilis. Addition of PRT added another \$100/donation in its cost. Cost-benefit ratio of whole blood PRT compared to current screens and interventions was \$1,276,000/quality-adjusted life-year (QALY; 95% confidence interval [CI] approximation 600,000-3,313,000). However, as residual risk of TTIs is already low in Canada, this estimated cost may be lower for developing countries where risk of TTIs is high. Hence, if PRT is adopted in Pakistan, it will be more cost effective than reported in developed countries. Moreover, interventions like discontinuation of viral or syphilis testing with screening for malaria only, during its seasonal peaks, may further increase the cost effectiveness for pathogen reduced blood products in countries like ours. Several of these technologies are commercially available and are user-friendly, hence can easily be acquired in Pakistan setting.

In conclusion, introduction of PRT is a paradigm shift in the prevention of TTIs. It is anticipated that PRT will revolutionize the blood safety programs and may replace conventional screening technology.

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