# Pathogen inactivation of platelet concentrates and fresh frozen plasma

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**ABSTRACT**

Transfusion of blood products carries the risk of pathogen transmission, despite careful donor selection and screening tests. This is due to viral transmission from window-period donations, the emergence of new pathogens such as variant Creutzfeldt-Jakob disease, for which routine screening tests are not yet available, and to bacterial contamination. Techniques have been developed to inactivate pathogens in both fresh frozen plasma and platelet concentrates. The relative benefits to the recipient, and the ease of incorporation into blood component processing are considered for the technologies currently available.

KEY WORDS: Blood-borne pathogens.
Plasma.
Platelet transfusion.

## Introduction

The risk of viral transmission by transfusion has been reduced with the introduction of careful selection procedures for blood donors, and with the implementation of screening tests for known bloodborne pathogens for each blood donation.[1]

However, although these strategies have significantly increased the safety of the blood supply in developed countries, there remains a residual risk of viral transmission. This is due to the so-called window period or lag phase between donor infection and the point at which seroconversion gives rise to a positive screening result. Nucleic acid technology has reduced this window period to between 8–11 days for human immunodeficiency virus (HIV) and hepatitis C infection.[2]

The second concern is the emergence of new infectious agents such as variant Creutzfeldt-Jakob disease (vCJD), the bloodborne hepatitis virus that is transfusion-transmitted (TTV) with unknown clinical significance[3] and West Nile virus, an outbreak of which occurred in New York.[4]

While the safety of the blood supply has improved and the risk of viral transmission has diminished, the opposite is true for bacterial contamination. This was the first recognised infectious hazard of transfusion and remains an ongoing problem. Sepsis and mortality can result from the transfusion of contaminated blood products. Platelet concentrates are especially implicated due to their storage at room temperature.[5] It has been estimated that the risk of acquiring an infectious disease following a transfusion of five blood components is approximately 2.7/1000 patients transfused.[6]

Products derived from fractionated plasma undergo viral inactivation steps as part of the manufacturing process, but these methods are inappropriate for more labile blood products such as platelet concentrates and fresh frozen plasma (FFP).[7] Recently, techniques have been developed to inactivate pathogens in both platelet concentrates and FFP,[6,8] and it is considered that the introduction of these into the manufacturing process would ensure the safety of these blood products to an even greater extent.

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## Infectious pathogens in blood

Blood can harbour many pathogens, including enveloped and non-enveloped viruses, bacteria, parasites and possibly prions.[7] Viruses can exist in blood as cell-free forms in plasma, cell-associated forms (either in or on leucocytes), or integrated into the genomic nucleic acids of cells such as leucocytes and megakaryocytes as a latent proviral form.[6]

Blood donations are currently screened for hepatitis B surface antigen, anti-HIV-1 and -2, anti-hepatitis C virus, and hepatitis C nucleic acid. A proportion of donations are also screened for anti-cytomegalovirus (CMV).

The incidence of viral transmission by transfusion is now so rare, however, that retrospective studies no longer can be used to assess risk levels. Mathematical models can be employed to give an indication of the level of risk. Estimates for the risk of viral transmission per unit, based on mathematical models, are 1/1.8 million units for HIV, 1/1.6 million for hepatitis C virus (HCV) and 1/220 000 for hepatitis B virus (HBV).[2]

There are also known bloodborne viruses that are not screened for, such as parvovirus B19, hepatitis G and various herpes viruses. While their clinical significance is unclear in the general population, there are certain categories of patient in whom transmission of these viruses is undesirable.[1]

Blood is also screened for antibodies to *Treponema pallidum*, the causative agent of syphilis. This is not thought to be of significant risk for transfusion purposes, but the continued inclusion of this test might serve to identify blood donors with undesirable lifestyles.[1]

Post-transfusion bacterial infection usually results from bacterial contamination, often due to the introduction of

bacteria from the donor's skin.[5] In several countries bacterial contamination is the most frequently encountered transfusion complication; however, the level is difficult to establish due to under reporting.[7]

Yomtovian has likened the problem to an iceberg,[9] because only the tip, representing the clinically significant cases, is apparent. In reality, the level of contamination is much higher, but not all cases produce symptoms, and not all symptoms can be attributed to a transfusion. Thus, the actual frequency of bacterial contamination is hard to assess, but is estimated to be approximately 1/2400 single donor platelet units.[9]

There are commercially available products to screen for bacterial contamination and their use is to be mandated in the USA. Bacterial contamination can be detected, but testing requires sampling at time intervals up to 48 hours, therefore a holding phase is required.[9] Blood collection bags that divert the first 20 mL of the donation minimise the introduction of skin bacteria.[10]

Creutzfeldt-Jakob disease and vCJD, so-called mad cow disease, are human forms of spongiform encephalopathy caused by infectious prion proteins.[1] Currently, no screening technique has been introduced into routine use, but possible testing systems are under development.[7]

Possible prion transmission route is thought to be via the B lymphocytes, a route suggested by limited experimental data that show that mice lacking mature B lymphocytes do not become infected with prions.[1] This data is the major factor in the decision to leucodeplete all donated blood in the UK and Ireland.[11]

Perhaps surprisingly, contaminating leucocytes are also considered as pathogens, and as such are targets for inactivation. This is because they can be the source of infection and give rise to an untoward transfusion outcome.[7] Their presence is undesirable for several reasons. The first is that leucocytes may harbour and transmit cell-bound infectious agents such as CMV and HIV, and may be involved in the transmission of prions. While this is a major consideration for pathogen inactivation, transfusion of contaminating leucocytes can also cause other side-effects such as febrile non-haemolytic transfusion reactions (FNHTR), graft versus host disease (GVHD), and, as a consequence of immune modulation, post-operative infections and tumour reoccurrence.

The introduction of leucodepletion as part of the blood processing scheme is designed to reduce the risk of immune and viral complications, but is not adequate to prevent transfusion-associated GVHD (TA-GVHD) or CMV infection.[6]

## Process requirements

An effective pathogen inactivation technique would achieve greater transfusion safety than any further refinements in microbiology testing because more pathogens can be inactivated than are currently tested for. The advantage of this is that as new pathogens enter the donor supply, its safety would be maintained by the further development of inactivation procedures.[6] However, the addition of any substance to blood products is not without risk, and several factors must be considered before a particular technique for pathogen inactivation is used routinely.

Areas that need to be studied carefully include the efficacy of the process, as ideally all targets need to be inactivated, and whether the blood product is damaged or altered by the process, as FFP and platelet concentrates need to be functional when transfused. The process used must be non-toxic to the recipient. The safety and efficacy need to be assessed by *in vitro* and *in vivo* tests, and successful clinical trials have to be undertaken.

It is expected that there should be some cost to health benefit in undertaking the procedure, as the introduction of expensive extra steps in the manufacturing process should provide additional safety and health benefits to the recipient.

Procedures currently at various stages of development can be loosely divided into two categories: photoinactivation and what are broadly classed as 'new technologies'. Photoinactivation methods are based on the use of photosensitisers, which are dyes that have light absorption properties if illuminated by a specific light source. This can lead to photodynamic reactions in which active oxygen species disrupt the viral envelope, or to photochemical reactions in which the pathogenic nucleic acid is altered irreversibly. So-called new technologies are based on compounds that modify cellular or viral nucleic acids irreversibly, but do not necessarily need an external energy source.[7]

## Platelet concentrates

Recognition of potential bacterial contamination of platelet concentrates due to the rapid replication of bacteria at room temperature led to the reduction in *in vitro* storage of platelets from 7 to 5 days.[6]

In addition to targeting the known viral risks, any system for pathogen inactivation used on platelets needs to act against a broad spectrum of bacteria to eliminate them and inhibit any regrowth during the shelf-life of the product. Platelet function needs to be intact, and there must be an adequate increase in the platelet count post-transfusion.[6]

*In vitro* platelet assays are commonly used, but there is some doubt as to whether or not they predict platelet recovery and survival post-transfusion. The most sensitive and specific assessment is thought to include morphology score, shape changes, hypotonic shock reversal, (which correlates well with recovery, but not lifespan) and adenosine triphosphate content. pH is also important because if it drops below 6.2 then platelet life span is reduced. Although assessment using these criteria is important, satisfactory results do not guarantee haemostasis, the clinical evaluation of which is difficult to assess.[6]

Gamma irradiation (25 Gray) to inactivate lymphocytes is used to prevent TA-GVHD following platelet transfusion.[12] This dose is insufficient to inactivate any microbial pathogens in the platelet concentrate. The dose that would be needed to achieve this would make platelets non-viable, and therefore this technique cannot be considered for pathogen inactivation.[7]

## Photochemical treatment

Several potential inactivation techniques applicable to platelet concentrates have been investigated. Merocyanine 540, which targets viral envelopes, leads to platelet

activation and serotonin release, so its use was not pursued further. Thionine also has pathogen inactivation properties when excited by light at 590 nm, and its use is being explored by German scientists.[6]

The main focus of interest has been on a group of compounds known as psoralens. These are planar furocoumarins, many of which are synthesised by plants, are present in vegetables such as celery, and have little known toxicity.

Psoralens bind reversibly with both single- and double-strand nucleic acids by intercalation, and then react with UVA light to inactivate pathogens by an irreversible photochemical reaction in which monoadducts and crosslinks are formed.[13] Different psoralen structures lead to differences in nucleic acid binding constants and therefore different pathogen inactivation efficiency.

Binding inhibits nucleic acid replication, transcription and translation. This is not specific to pathogenic DNA but is beneficial,[7] as nucleic cell function is not vital for transfused platelets and nucleic acid disruption in any residual leucocytes will diminish the occurrence of FNHTR, TA-GVHD and adverse immune responses.

The first psoralen studied was methoxypsoralen (8-MOP) which targets all three viral forms, as well as Gram-positive and Gram-negative bacteria and protozoa. As a result of the photochemical reactions with UVA light, adduct formation with nucleic acid is observed, but binding is of low affinity and competitive binding with plasma proteins is seen. Long illumination times, reduced oxygen levels and suspension of platelets in a non-protein medium are needed to achieve pathogen inactivation. This is not satisfactory for routine use so this compound has not been developed further.[6]

Another psoralen studied is a synthetic compound known as aminomethyl trimethyl psoralen (AMT). This is effective for viral inactivation, but its action against bacteria is unknown. However, considerable UVA illumination is needed and free radical quenchers such as rutin must be added to prevent the active oxygen species formed damaging the platelets. This adds to the complexity of the system. Toxicology studies also reveal that residual AMT (the remnants following photochemical treatment) has mutagenic potential in the absence of light.[6]

A number of psoralens have been synthesised and from these an aminoalkylated psoralen, originally termed S-59 but now known as amotosalen,[14] was chosen because of its favourable toxicology profile. Structurally, it combines the characteristics of 8-MOP and AMT.[4]

Infectious pathogens are rapidly inactivated due to the high binding affinity of amotosalen with nucleic acids. Using a platelet additive solution to reduce the plasma concentration, platelet function is maintained. Also, there is no need for the addition of quenchers.

The pathogen inactivation potential of amotosalen and UVA light was determined by adding high levels of pathogens to platelet concentrates, and using bioassays to assess the level of infectivity after treatment.[13] HIV-1, hepatitis B and C, and examples of both Gram-positive and Gram-negative bacteria are all inactivated following illumination by 3J/cm$^2$ UVA light.[13]

*In vitro* platelet function was assessed by comparing treated and non-treated platelet concentrates. Treated platelets showed similar results to non-treated platelets, apart from a difference in P-selectin expression, which may be a predictor of shortened survival post-transfusion.[6]

Clinical trials have been completed successfully, firstly using autologous radiolabelled platelets in healthy volunteers. Although the results showed decreased platelet recovery and lifespan, they were tolerated without adverse incident. Treated platelets have also undergone trials in patients with thrombocytopenia, which proves that haemostatic function is maintained.[7] Extensive evaluations have been undertaken both in Europe and in the USA with no problems observed in haemostatic ability, recovery or survival.[15]

There has been some concern about whether or not photochemical treatment of platelets will lead to the production of neoantigens, which could cause problems for patients receiving multiple platelet transfusions, but evidence produced so far does not indicated this.[6]

The INTERCEPT system, which employs amotosalen, has been developed by Cerus in collaboration with Baxter Healthcare.[16] It inactivates pathogens in platelet concentrates by what is known as Helinx technology, and is the only system ready for the commercial market. A phase III trial (the euroSPRITE trial) has been completed using pooled buffy coat platelets, and no differences were observed in haemostatic function or adverse events between treated and non-treated platelets.[17]

The system has obtained a CE mark and process evaluation for European blood bank good manufacturing practice requirements has been undertaken.[16] Currently, introduction of this technology is awaiting government approval. An additional benefit of the INTERCEPT system is that gamma irradiation is not required, as the inactivation technique prevents GVHD.

In the USA, platelets are prepared by apheresis or from platelet-rich plasma derived from whole blood; therefore, due to this variance in production, further clinical trials are required before it can be considered for this market. It is possible that pathogen inactivation may be used in addition to detection tests.[18]

## Fresh frozen plasma

Fresh frozen plasma is used to treat congenital coagulation deficiencies when no specific coagulation factor is available, and also for acquired coagulation deficiencies because it contains all the coagulation factors and inhibitors normally present in plasma. First-time donations are not used to prepare FFP in order to minimise viral risk.[11]

Viruses are the main target for pathogen inactivation in FFP, especially those that can exist in a cell-free form in plasma. Any inactivation technique employed needs to maintain the functionality of the product at an adequate level. This can easily be assessed *in vitro* by clotting screens that measure coagulation pathways (e.g., prothrombin time), by coagulation factor assays that measure the level of specific factors, and by assays that test for the presence of inhibitors of haemostasis (e.g., antithrombin III, and proteins C and S).

Tests can also be performed to detect markers which signify activation of the product.[7] *In vivo* tests used to ensure the efficacy of the product include pharmacokinetic studies in volunteers who have received an FFP transfusion, and also by assessing the response when the product is

transfused into patients with known coagulopathies.[7]

Viral inactivation of FFP is more advanced than for platelet concentrates, as there are currently two virally inactivated products available in the UK. The two processes used are methylene blue treatment and solvent detergent treatment.[11]

## Methylene blue treatment

Methylene blue, in combination with visible light, has pathogen inactivating properties. It is a hydrophilic dye that undergoes a photodynamic reaction with light to form a reactive oxygen species. This leads to oxygen depletion and cell damage. Viruses are killed by the energy transfer reactions involving oxygen in this excited state.[7]

The process inactivates enveloped viruses by damaging their nucleic acids, preventing replication; however, it is unclear whether or not non-enveloped viruses are inactivated.[11] There is some evidence to suggest that methylene blue is effective against parvovirus B19,[7] and it is estimated that 50% of prion proteins are removed by the filtration step that is part of treatment.[19]

Methylene blue treatment affects several labile plasma products such as FVIII, but the levels obtained, although reduced by 15–20%, remain within acceptable limits;[8] however, concern has been raised that only plasma from group A donors, who are known to have higher levels of FVIII, would maintain acceptable levels after treatment.[19] Fibrinogen is also susceptible to photo-oxidative damage, and some reports have suggested up to 39% reduction in activity.[20]

As methylene blue is not effective against cell-associated viruses, any residual cells are first removed by filtration, and then the dye is added and the pack illuminated. Techniques are now being developed so that both sides of the pack can be illuminated at the same time, and up to three packs processed together to speed up the procedure.[19]

There are concerns about the toxicity of methylene blue, but it has been used therapeutically at much higher levels, with no resulting toxicity observed, and there are processes available to remove the methylene blue if required. Over two million methylene blue-treated plasma donations have been transfused across Europe, without adverse reaction;[11] however, it is no longer accepted by European regulatory authorities, due to concerns about mutagenicity, and is currently only used in the UK.[14,20]

Owing to the unknown risk of vCJD transmission, methylene blue-treated plasma for use in neonates and children born after 1 January 1996 has been available in the UK since July 2002.[21] This product was chosen as it is the only single-unit, pathogen-inactivated plasma available.

In order to limit donor exposure further and allow additional product criteria to be developed, the National Blood Service (NBS) uses a panel of accredited donors for the preparation of blood components for paediatric and neonatal use.[22]

Soon, the plasma used will be sourced in North America, following Department of Health recommendation. If this is frozen prior to import and methylene blue treatment in the UK, a further loss in coagulation factor activity is expected.[23]

Owing to a lack of data on clinical efficacy and tolerance, the equivalency of methylene blue-treated plasma and FFP has not been demonstrated satisfactorily.[24]

## Solvent detergent treatment

The other virally inactivated product available for use in the UK is solvent detergent-treated FFP. This is used widely in Europe, and in countries such as Norway and Belgium its use has completely replaced that of FFP.[8] In addition, the Food and Drug Administration has recommended approval of this product in the USA.[8]

Lipid-enveloped viruses can be differentiated from protein-coated viruses by the use of solvent ethyl ether and the detergent Tween 80. This forms the basis on which viral inactivation using solvents and detergents has been developed. Different solvent and detergent combinations have been evaluated for their ability to inactivate enveloped viruses without detriment to FFP function.

The method currently in use involves treatment with 1% Tri (N-butyl) phosphate (TNBP) and 1% Triton x-100.[8,25] These are removed using vegetable oil extraction and reverse phase chromatography with a C18 resin during the purification process, and the levels remaining are not expected to have any clinical side effects.

Solvent detergent treatment is effective against the majority of transfusion-transmitted viruses (e.g., HIV, HBV and HCV) as these are enveloped viruses. Solvent detergent treatment is not effective against non-enveloped viruses, which means that hepatitis A (HAV) virus and parvovirus B19 may not be inactivated by this process. It is also suspected that prion proteins are not inactivated by this treatment.[26]

Solvent detergent treatment is used to process large pools of ABO-identical plasma donations, and some 600–1500 donations are pooled in Europe and up to 2500 in the USA.[11]

Presence of HAV and parvovirus B19 will be diluted in the process and it may provide partial protection due to the presence of antibodies to these viruses in the plasma pool.[27] There have been clinical cases of parvovirus seroconversion reported following the transfusion of this product.[7]

Pooling the plasma may reduce the risk of post-transfusion complications such as allergic reactions and transfusion-related acute lung injury (TRALI).[11]

As seen with the use of methylene blue, solvent detergent treatment results in a decrease in coagulation factor activity.[27] FVIII activity is reduced by over 20% and levels of protein S and ∝-2 antiplasmin fall by more than 50%. The process also removes high-molecular-weight von Willebrand factor multimers, which makes it particularly suitable for the treatment of thrombotic thrombocytopenic purpura (TTP).[27] As the batch product is treated in its entirety, the levels of coagulation factors are consistent throughout.[11]

The major concern about the use of solvent detergent-treated FFP seems to be that it is a pooled product. Although this may convey some benefits, the risk of parvovirus B19 transmission may mean that it is not the product of choice for certain at-risk categories of patient, such as pregnant women and patients with severe immunodeficiencies and haemolytic anaemia.[8]

Solvent detergent-treatment only inactivates enveloped viruses and although the process reduces the viral risk from currently known pathogens, there is always the risk that newly emerging ones may not be inactivated. The use of a pooled product then provides the potential for widespread transmission.[8]

It has been suggested that in order to satisfy all categories of patient it may be necessary to stock a variety of FFP in the blood bank.[8]

## Pharmacoeconomics

While pathogen inactivation is considered to be the way forward, the pursuit of zero risk must be balanced against cost-effectiveness.

Pharmacoeconomic studies have considered several factors. The selection of donors and the screening of donations already includes a high safety margin, thus any further improvements will be slight, hard to prove and expensive, resulting in a marginal cost:benefit ratio.

Clinical trials do not necessarily show equivalency with non-treated products. Greater volumes of raw materials (up to 30%) may have to be used in the manufacturing process to achieve an 'equivalent' product. This has obvious economic implications, and supply may be a problem with an ever-decreasing donor population.[28]

Cost effectiveness studies in this area are limited but, due to the high mortality factor associated with patients receiving blood products, it is estimated that the transfusion of virally inactivated FFP, instead of a standard pack, prolongs survival by just one hour and 11 minutes.[29] However, this slight benefit is probably negated by the hazards associated with the inactivation process.

Obviously, there are more health benefits to be gained from pathogen inactivation of platelets, especially if the need to irradiate for selected patients at risk from TA-GVHD is removed, and the problems due to bacterial contamination are eliminated. Currently, cost effectiveness must be considered for each product as each is processed differently. The ideal approach would be the use of one all-embracing technique on the complete donation before it is split into components. The development of new techniques using riboflavins may offer pathogen inactivation techniques appropriate to FFP, red cells and platelet concentrates.[15,30]

Whichever inactivation technology is chosen, its introduction will have implications for NBS personnel, and this ongoing issue is likely to result in changes as research is put into practice. It has been suggested that it may not be necessary to employ sophisticated screening tests in tandem with pathogen inactivation processes, and some savings could be made by discontinuing less-informative screening tests.[31]

Government legal advice is that any patient who becomes infected following a transfusion may have the basis of a claim against the NBS if technology for pathogen inactivation is available but not used.[32]

Errors in the chain of events leading to a transfusion contribute significantly to adverse transfusion outcomes; however, the introduction of pathogen inactivation techniques will not lead to a reduction in such events. It has been suggested that strategies to improve the level of safety in this area would be far more cost-effective, and these should be considered.[33]

The current tendency towards the introduction of procedures thought to increase transfusion safety appears to be driven by public concern, media frenzy, politics and the fear of litigation. These may be the driving force behind the introduction of new techniques, rather than an evidence-based, cost-effective scientific decision, but such techniques may move zero-risk blood transfusion a step closer. □

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