Pathogen reduction marches on

Several articles recently about pathogen reduction (PR) have highlighted the increasing interest in this topic. If we had a way to render blood components—all blood components—free of infectious particles, it would be a wonderful step forward in providing products for our patients that could be life-saving but with very low risk of transfusion-transmission of disease. In the last issue of PLUS (Fall, 2015), we noted a Perspective article in the New England Journal of Medicine calling once again for a concerted effort to mandate already approved PR in plasma and platelet products, a plea first made in 2008 to the Secretary of Health and Human Services by one of his own advisory committees. One main stumbling block has to do with exactly who will pay to implement this, since hospitals and payers, including the U.S. government, are strapped for cash and not eager to increase financial commitments.

Meanwhile, information continues to accrue regarding PR of both viruses and bacteria (see references.) Workers from Colorado and France point out that the effectiveness of testing for infectious diseases relies on there being a certain minimal level of the pathogen, and those below that level will be falsely negative but may be, or become, infectious. Estimates of this “window period”, based on donor seroconversion studies, appear to be 9.5 days for HIV, 8.0 days for HCV and 38.3 days for HBV. One way to provide an additional layer of safety is through the use of a broad spectrum PR process. The authors of the first paper below utilized a Mirasol-based system with riboflavin as a photo-sensitizer and UV light as a “killer”, so to speak. They tested it against a broad range of viruses including HAV, HCV, influenza A virus and LaCrosse virus as well as against recommended model viruses—encephalomyocarditis virus, pseudorabies virus, Sindbis virus and vesicular stomatitis virus. These thus include a broad family of enveloped and non-enveloped viruses.

This technique reduced viral loads, in most cases, by several logs. HAV, not usually associated with transfusion-transmission, was only reduced by 1.8 logs. Previous studies with this method had shown a reduction in both intracellular and cell-associated HIV by 4.5-5.9 logs. The authors postulate that the use of PR, admittedly expensive, might replace all the expensive testing for bacteria and viruses now in use, but that seems a long ways away. The FDA has not been willing to allow cessation of a previously mandated test for blood-borne pathogens, witness syphilis testing.

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Cover photo: End-release labeling of platelets. Photo by Amanda Romney/American Red Cross.

This issue of PLUS was written by Dr. Robert (Bob) Westphal.
Blood bankers from Frankfurt, Germany, with the collaboration of the U.K.’s national bacteriology lab for the transfusion services, have looked at the effectiveness of PR against selected bacterial strains in whole blood, platelet apheresis and buffy-coat pooled platelet concentrates. (second reference.) The PR technology used was Cerus Labs’ INTERCEPT system, another photochemical system. Units were inoculated with bacterial species in concentrations of 100 and 1,000 colony-forming units (CFUs) per bag. Each test component was inoculated with a single species, these being selected for their relevance in clinical transfusion medicine, having been identified by the Paul-Ehrlich Institute to have caused severe transfusion reactions. Buffy coat platelets were PR at either 12 or 35.5 hours. Apheresis platelets were PR at 12 hours. Inoculuae used were: *Bacillus cereus*, two strains of *Klebsiella pneumoniae*, *Serratia marcescens*, *S. aureus* and *S. epidermidis*, *Streptococcus pyogenes* and *Yersinia enterocolitica*. Bacterial testing was done using standard bacterial alert systems currently used for platelet concentrates.

The INTERCEPT PR system was not 100% effective in the buffy coat experiments against high concentrations of certain *Klebsiella* strains, nor against spore-forming strains of *Bacillus*. One critical observation was that the period between donation and PR should be minimal, so as to avoid growth. The authors recommend that if PR cannot be initiated immediately after component production the addition of a rapid bacterial test at Day 4 or 5 should be done.

What about platelets that have been re-suspended in additive solutions? Do they survive the PR technique in adequate numbers, compared to plasma or buffy coat stored platelets?) Using the Mirasol PR technology (riboflavin plus UV light exposure) staff from Terumo in the U.S, Spain, Belgium and Minnesota reported on an observational study on corrected count increments (CCIs) after PR treatment in platelet additive solutions PAS-C or PAS-E. Post-transfusion samples were taken 30-75 minutes and 18-36 hours after transfusion. The CCI is a standard measurement for expressing an increase per dose of platelets accounting for the body surface area of the patient. There were 77 Mirasol treated products transfused to 20 patients, one of them a long-term platelet refractory patient who was withdrawn from the study. None of the patients were actively bleeding and 45 of the transfusions were with pre-transfusion counts of $< 20,000 \times 10^9/L$. Transfusions consisted of 5-6 pooled buffy coats.

The two PAS have equivalent amounts of chloride, phosphate and citrate, but differ in that PAS-E has 8 mM/L less sodium chloride but has 5 mM/L of potassium and 1.5 mM/L of magnesium. The PAS-E products had platelet counts and CCIs that were significantly higher than those from PAS-C; however, both demonstrated platelet transfusion success rates comparable to studies in plasma-suspended platelets. 78% of the transfusions classified as successful at 1 hour with CCIs higher than 7500 and 63% were higher than 4500 at 24 hours. No adverse events were observed with any transfusion, and no contaminated products were detected by BacT/ALERT.


A need for validation and standardization in pathogen reduction studies

Pathogen reduction is much talked about these days, as witness the articles mentioned in this edition of PLUS, and they will continue to be as we all struggle to improve blood product safety and to reduce costs. These two objectives are, mostly, at odds with each other, at least currently. The authors of an editorial in a recent issue of Transfusion (see reference) had some cautionary words about the current status of studies in PR in bacteria.

Published results of the several different technologies used are not really comparable since they have not been done with standardized techniques, pathogen strains or platelet products. As well, there are recognized weaknesses in the use of some technologies for certain pathogens. Prions are not inactivated and bacterial spores, such as from Bacillus species are not. In the studies of Schmidt et al (see accompanying article), the authors noted failure to adequately inactivate one Klebsiella species and Bacillus cereus, a spore-former, probably because the inoculae exceeded the published capacity of the inactivation process. Other previously published studies have shown failure of inactivation to sterility with several different methods of light inactivation, possibly for the same reason.

The editorial writers go on to propose some standard criteria for PR studies to enable realistic data that can be used to evaluate different methods and practices with bacteria. 1. Standardize outcomes and use sterility as determined by culture of a large volume sample, 8 ml. 2. Use standard and clinically relevant bacterial strains known to grow in platelet products. There are WHO and ISBT registries for this purpose. Klebsiella organisms are especially important since they grow rapidly in platelet preparations and were the most frequent cause of fatal sepsis before the advent of bacterial screening. 3. Bacterial growth varies in different host’s blood or plasma, so at least three different donor sources should be used for each study. 4. There should be consistency in the number of colony-forming units (CFUs) in the various inoculae, and they should adhere closely to what occurs in nature. The use of 1,000 CFUs, added soon after collection, is an excessive number, the range of 1-100 is much more likely, in reality.

Other things, such as the delay before administering PR materials, are also critical and need to be agreed upon. As well, the effects of the transfusion of endotoxins from killed/inactivated pathogens need to be understood.

Benjamin RJ, Wagner SJ. Bacterial pathogen reduction requires validation under conditions of intended use. Transfusion 2015; 55: 2060-2063.
The bug was in the bag!

In 2008, an article in the *New England Journal of Medicine* reported on 3 cases of dengue in a Singapore hospital traced to a dengue-positive donor. The cases might have gone unnoticed except for the fact that the donor had been asked to report any acute illnesses after donation. He did so after developing a fever 2 days after donation and alerted authorities who promptly pursued an investigation of all recipients of his RBCs, platelets and FP. In general, donor screening for dengue is not established anywhere, except for occasional episodes of screening of selected donor groups in the face of an outbreak, such as has occurred in Puerto Rico with the American Red Cross.

Another article from Singapore appeared in the July edition of *Transfusion* (see reference) describing transmission of dengue from a single unit of RBCs, given by a first time donor to a patient whose Hgb level had dropped to 8.4 from 12.8 g/dl from rectal bleeding after suffering a hypertensive hemorrhagic stroke. Four days later the patient was noted to be febrile with a normal platelet count, and 3 days after that the count had fallen to $16 \times 10^9$ per mm$^3$. She then received platelet concentrates because of the recent rectal hemorrhage. [The article doesn’t state if bleeding recurred.] To confirm the donor as the source of the dengue, the donor’s (fortunately) un-transfused plasma and the patient’s plasma were tested for residual dengue using reverse transcriptase-PCR (polymerase chain reaction). The results were positive in both cases, and sequencing demonstrated dengue virus type 2 in both, and with 100% positive sequence homology between the two of them. Both were clearly related to the then-circulating strain in the Singapore outbreak.

We routinely screen for West Nile Virus, of course, and 6 or more other infectious diseases, and rely on donor histories to help with still others. Are we going to routinely screen for dengue, chikungunya, Lyme disease, babesiosis? What about, in the U.S., other tick-borne diseases, such as erlichiosis, anaplasmosis, Powassan if it emerges? All of this testing will cost a lot of money, and time, and blood banks and hospitals have trouble now having enough of both. This points up the importance of an editorial noted in this fall’s edition of PLUS: we must find the way to develop and implement effective pathogen reduction for ALL of our blood components.

The discussion concerning the use of “old blood” has not been entirely settled, and likely never will be totally for everyone who uses or provides products for transfusion medicine. As has been noted in some journals, including the *New England Journal of Medicine*, *Transfusion*, and others, large-scale randomized, controlled trials have been difficult to carry out. Despite the presence of red cell “storage lesions”, the use of older blood in transfusion is not predictably a cause of failure. More work recently has focused on the fact that less blood seems generally to be as useful as—or better than—more blood, which is to say that we have changed the “transfusion trigger” in most cases of blood use.

The storage lesion has many possible fathers, so to speak, including lipid peroxidation, membrane loss, and exposure of thrombogenic substances in the membrane. There are diminished levels of ATP. The amount of glutathione—an important element of protection from oxidation as well as Hgb oxidation—is also reduced. The result of these changes, microscopically speaking, is the shape changes to the red cell with aging, resulting in formation of echinocytes. These RBCs have decreased amounts of membrane and decreased deformability due to protrusions of cell membranes that look somewhat like blunted horns. Seeing these under the microscope, one can believe that they are not easily passed through the microcirculation.

Workers from three hospitals in Switzerland and from a bioengineering department in Houston developed a method of correcting this harmful shape change in *vitro* and testing it in an artificial microvascular network (AMVN). They used leukocyte-reduced blood that was 6-7 weeks old (AS-1 leukoreduced RBCs outdate at 6 weeks in the US). In Switzerland two types of SAG solution that outdate at 6 or 7 weeks were studied. One part of the RBCs was suspended in 9 parts of a 1% human serum albumin suspension, mixed and washed for 10 minutes, then centrifuged. Cells were examined in wet preparations by light microscopy and given an echinocyte score and various chemical and physical analyses were carried out.

A return of echinocytes towards normal discocytes was illustrated in actual photographs, as well as in reductions seen in the echinocyte scores of the preparations. No such recovery was seen in washing the echinocytes in normal saline, buffer or “whole” plasma. The normalization of shape in red cells did not result in improved RBC deformability as measured in the laboratory by ektacytometry; however, it did improve suspension viscosities at low shear rates in a Couette viscometer. It also measurably improved the ability of the treated RBCs to perfuse the AMVN, although it’s not exactly clear how to compare the AMVN with that of a severely ill human. However, actual transit of albumin-washed stored RBCs at the level of 5 µ capillaries in the AMVN illustrated some RBC plugging similar to that of untreated/unwashed RBCs. This was not seen with fresh RBCs.

The study clearly shows improvement in echinocyte shape change by washing in 1% albumin solution. Washing in plasma had no similar effect. The authors believe that this may have significant positive effects that would improve or rejuvenate the deformability and circulation of RBCs at the end of their shelf life. They state that might improve blood circulation under conditions of massive transfusion with “old blood”, thereby improving clinical outcomes. Apparently, not all units are similarly affected, and the authors suggest limiting the procedure to RBC units with a high degree of echinocytosis. How practical this is remains to be seen. Given the costs involved, the other demands on transfusion medicine resources, and the fact that we are using considerably less blood for transfusion these days, this may not be something we’ll end up doing. But, it is a valuable contribution to the “old blood” dilemma.

About 25-30 years ago, prompted by a public very anxious about transfusion-transmission of HIV and HCV, around 8.5% of the red cells collected for transfusion in the U.S. were autologous in nature. Preoperative autologous donation (PAD) then accounted for over 1,000,000 units/year, and a large number of these were not used, especially those that were collected “just in case”. Prospective patients and their families wanted to use their own blood, or that of relatives and trusted friends, and not much thought was given to the timing of PAD and its effect on the patient’s recovery. Some blood bankers at the time stated that the human body was still the best place to store human blood, that PAD was overdone. For those blood banks, blood collection and hospital workers who lived through that terrible experience, it was an exceedingly difficult time. Markedly improved infectious disease testing gradually served as reassurance to prospective blood recipients.

By 2011, this number was down to 0.7% and almost half were never used. The history of PAD is complicated and is the subject of an excellent review by U.S., Canadian, and European transfusion medicine experts in a recent issue of Transfusion Medicine Reviews (see reference). The authors review the risks and benefits of PAD, the safety concerns and specific guidelines to make better use of them, and their cost-effectiveness in terms of quality-adjusted life years (QALY). In most European countries, the demand for—and use of—PAD was never as strong as in the U.S., and much stricter criteria for their collection and use were in place. HIV infection rates were not as strong in some of these countries, so the hysteria surrounding the issue may have been less. There are potential benefits for the use of autologous donation but when first introduced the primary focus was on the elimination of allogeneic transmitted disease. The authors thoroughly summarize the potential benefits, and risks.

Potential risks include possible identification or labeling errors, testing losses and logistical losses due to timing, transportation etc. There is an increased risk of perioperative anemia and hypovolemia, both avoidable reactions, as well as donation reactions in people with cardiac or respiratory disease. PAD is conducted at a decreasing number of sites, since it is a costly procedure for collection and lab staff. The authors expand on these and other issues, including the fact that such provisions may exceed the generally accepted cost of a QALY, as noted above. And since a history of infectious disease, including hepatitis and HIV infection, does not disqualify some donations, there is a risk of a real catastrophic event if such a unit is erroneously administered, or in case of a laboratory accident. Collecting blood from a donor who is otherwise unqualified, for any number of reasons, also leads to much higher levels of donor adverse events by 10-12-fold.

There are significant timing concerns with regard to PAD that, if ignored, can affect the health of or outcome for a patient. Some collection schedules and volumes have led to an actual increase in the use of homologous blood in order to maintain a relatively “normal” Hgb level. Given the marked reductions in transfusion-transmitted infections, PAD as such is harder and harder to justify, and with the (hopefully) accelerated development and implementation of effective pathogen reduction techniques for blood components, it may become a thing of the past. Cell salvage during surgery and aggressive approaches to pre-operative anemia will continue to be helpful in avoiding homologous transfusion, as well as avoiding PAD.

Erythropoietin vs. transfusion in cardiac surgery

As our population ages, more people are coming to the hospital for complex surgical procedures, many of which involve significant blood loss. Some are already anemic, due to other comorbidities or to age and diet. Not everyone can be handled using emerging guidelines for patient blood management that allow their Hgb level to sink to 7 or 8 gms/dl. Preoperative transfusion, of course, can help this; and so can steps taken a few weeks before to treat the anemia. These latter efforts have included the use of erythropoietin (EPO) in various schedules in the days leading up to surgery.

The minimal effective EPO dose is not known, and certainly varies from person to person. Protocols have varied from a single large dose given the day before surgery, plus another the day of, to more complicated efforts involving multiple doses over multiple days, or even weeks. Many such studies have targeted only specific subgroups of potential patients, such as valve surgery. The pressure to reduce both costs and hospital length of stay (closely related, of course) tend to ignore the fact that injected EPO does not have an immediate onset. The authors (from hospitals in Rome and in the Bronx) had previously used a schedule involving injections on days -2, -1, the day of, and the day after the surgical procedure, a logistically difficult and prone-to-error schedule.

They devised a new schedule that employs a much larger single dose of EPO, 80,000 units the day of admission (which was 2 days prior to surgery in their study). They performed a single-blinded, prospective, randomized study on 600 consecutive patients with Hgb levels of 14.5 g/dl or less. They could thus compare results in anemic (Hgb < 13.0 preoperatively) vs non-anemic patients. All of the surgical procedures were carried out at the hospital in Rome. All types of antiplatelet agents and anticoagulants were discontinued 5 days prior to surgery. A 1:1 allocation of patients to test vs control kept the group sizes equal, but the authors (surgeons, anesthesiologists) were not aware of the assignment until the end of the study.

A trigger Hgb for transfusion was set at 8.0 g/dl, and any patient with a preoperative level <9.0 g/dl was referred for evaluation and not part of the study. All patients, control and study, received oral iron supplementation and preoperative levels of ferritin and transferrin were obtained as well. Of the 642 patients recruited, 42 were excluded based on exclusion criteria, primarily renal function, and 10 refused to participate. Thus, there were 300 patients in each group. A very complete list of baseline characteristics (total 28) and procedures and intraoperative variables (total 28) show no differences between the two groups.

In the EPO group, 17%, versus 39% in the controls, required transfusion, p< 0.0005. The distribution of the number of units transfused also was shifted to lower numbers in the EPO study group. Among the patients with preoperative Hgb levels >13 g/dl, there was no difference in the incidence of transfusion, these patients being the preoperatively non-anemic arm of the study. In addition, there was no difference in the all-cause mortality rate at 45 days (3.0% EPO vs 3.33% control), and the adverse event rate at 45 days was similarly not significant (4.33% vs 5.67).

The authors conclude that in anemic patients (Hgb<13.0 g/dl) a single large dose of EPO 2 days before surgery is effective in reducing the incidence of allogeneic transfusion and does so without increasing adverse events.

As probably everyone reading this knows, babesiosis is an intraerythrocytic parasitic disease caused by Babesia microti and is transmitted by deer ticks. In patients who are healthy, it may cause only mild flu-like symptoms; however, in elderly or vulnerable immunosuppressed individuals it can cause a severe hemolytic anemia, even death. It is endemic, and spreading, in the northeast and north central United States, more so in the former, and there are reported frequencies in the Pacific Northwest and in several northern European countries, where the causative parasite is Babesia divergens. About 96% of the nearly 1,000 cases reported in 2012 were from Connecticut, Rhode Island, Massachusetts, New York, New Jersey, Minnesota and Wisconsin. There are no licensed screening tests for B. microti, but several assays are available. Currently, about a dozen cases a year of transmission-transmitted babesiosis are recorded. Donors are asked if they have ever had it, and if so they are permanently deferred. Most donors, until recently, have never heard of it.

Three years ago, American Red Cross began testing donors in targeted counties of Connecticut and Massachusetts using a fluorescent antibody (Ab) test and a polymerase chain reaction (PCR) in tandem, the former looking for antibodies and the latter for parasitic DNA. The authors of this current paper, including those from the ARC testing labs (see reference), developed a decision tree model to assess the cost effectiveness and comparative effectiveness of testing approaches. They modeled four different testing strategies: universal (all donors) Ab screening; universal PCR; universal Ab and PCR; and, risk-targeted Ab and PCR—that is high risk donors with a positive answer to having had babesiosis. They used the model to predict the number of transmission-transmitted cases, cases with complications, cases averted, and quality adjusted life-years (QALYs). The analysis also provided for each strategy: the per-donation cost, cost of waste (number of units discarded) and a waste index (number of units wasted / number of true positives). Thus, a complicated model was used for the analysis in 4 endemic states: Connecticut, Massachusetts, Wisconsin and Minnesota. They also provided for a sensitivity analysis of the performance of these assays in transfusing patients with low vs. high risk, a difficult analysis given variable transmission rates and lack of information concerning recipient health status—such as asplenia, immunosuppression, age, and other comorbidities.

Using universal PCR alone in these 4 endemic test states would result in preventing 24-31 transfusion-transmitted babesiosis cases /100,000 units transfused. Adding universal Ab testing to this would prevent 32-44 cases /100,000 units transfused but raise the cost-effectiveness ratio from $26,000 – $44,000 per QALY to $54,000 - $83,000 per QALY. A QALY, by World Health organization definition, is about 3 times the average annual salary in a country, this latter being about $50,000 in the U.S., or $150,000. This latter strategy has a waste index of 0.05, compared to one of 0 for the PCR alone. Remember, the waste index is the ratio of falsely positive discarded units divided by the number of true positives. The Ab test has more false positives than PCR. Remember also that this is a model that uses previously reported numbers from various studies, not an actual study in the 4 states noted.

Nonetheless, the study clearly illustrates that—if one accepts the model—universal PCR testing for babesia in endemic states is a cost effective strategy at a threshold of about $50,000 per QALY. Addition of universal Ab screening increases the cost effectiveness ratio but also increases the likely number of cases prevented. Now the question is whether or not this will become a required test for United States blood centers and hospitals. If so, will it be universal, or limited to the previously described endemic states? Or will it include summer travelers to those states from other regions? Who will pay for it? As we provide for more and more specific testing, these questions, and many others, will become paramount. All the more reason for rapid development and deployment of pathogen inactivation/pathogen reduction techniques.

Clearly, as suggested by words from the Frost poem, we have a long way and many miles to go before we sleep.

Bish EK, Moritz ED, El-Amine H, Bish DR, Stramer SL. Cost effectiveness of Babesia microti antibody and nucleic acid blood donation screening using results from prospective investigational studies. Transfusion 2015; 55: 2256-2271.
Platelet-rich plasma: a new fountain of youth?

It’s not exactly clear how the use of autologous platelet-rich plasma (aPRP) for orthopedic healing purposes first got started. A paper in 1998 invoked the growth factor enhancement effect in bone grafts in facial surgery, and by the years 2006-2010 there were numerous articles in orthopedic, dental and sports journals attesting to the “healing properties” of aPRP. We do know that platelets contain a reservoir of growth factors and cytokines that—among other things—may promote healing. After the publicity surrounding its use as a healing factor by a number of famous athletes, including Tiger Woods, the use really took off. Various means of collection, preparation, storage and administration have been used, and there are no agreed standards that can be used to define dosage, safety, effectiveness, cost, and related matters. There also are questions about licensing, who is allowed to make it, who can charge for it, and how it is reimbursed—by folks other than elite athletes, that is.

Platelets are released from the bone marrow as small cell fragments without nuclei. The cell membrane is rich in glycoprotein receptors that bind to sites of tissue injury, and when they do that, they release their granule contents into the immediate area, including hemostatic molecules such as fibrinogen and von Willebrand factor. Other granules contain interleukins, beta thromboglobulin, platelet factor 4, adhesion molecules and at least four growth factors for vascular endothelium, stroma, and epidermal cells. Thus, platelet-derived biologic mediators have two basic effects: recruitment and activation of related cellular elements/mechanisms, and angiogenesis regulation—the promotion of new blood vessels in an orderly manner.

There are a variety of technologies in use for producing aPRP from autologous anticoagulated whole blood, including everything from apheresis and cell-salvage techniques to direct manual aspiration of the product from a centrifuged bag. Most of the methods are now commercially available, all with different claims of percent recovery, content of platelets, and relative amounts of plasma, buffy coats, and red blood cells. To what degree the various processes of product preparation activate platelets and cause degranulation, loss of potency, etc., has not carefully monitored.

The authors from the University of Minnesota (see reference 1) recently published a review of this issue that includes some of the original articles describing preparation and use that identified twelve randomized controlled trials (RCTs) and one controlled cohort study. Four RCTs were of lateral epicondylitis (tennis elbow), two of Achilles tendinopathy, two of anterior cruciate ligament injury (knee), and five of rotator cuff injuries (shoulder). Four of the RCTs reported some benefit from aPRP vs. controls, while eight reported none. All protocols used a different method for preparing the aPRP, or used a different method of delivery or application. The authors conclude that there are no standardized criteria that define aPRP since these different techniques vary widely in terms of platelet counts, techniques involved in preparation and administration, and concentration of the desired molecules in the final product. The authors suggest that the expertise of transfusion medicine and blood banking should be used to develop and implement protocols for the production and administration of aPRP, including quality control measures and methods for legitimately and reproducibly measuring their effects.
An accompanying editorial from the University of Vermont, in this same issue, agrees with the above and has some additional thoughts on the practice. The authors point out that there are also several “non-clinical” issues that are confusing the picture, and the practice. They note that the Cochrane Reviews (see discussion in previous PLUS article on red cell transfusions in surgery) have found no evidence of clinical efficacy for the use of aPRP as currently described. In the meantime, and despite this, many patients with osteoarthritis of the knee are offered these injections as a means of putting off knee replacement surgery. Additionally, aPRP has also become increasingly used in a new trend: facelift procedures involving a large number of injections over the entire face. The authors note a newspaper report of such a “vampire face-lift” provider being arrested after the death of a patient/victim.

Who is it that will regulate the use of aPRP? The FDA regulates biologics via the Center for Biologics Evaluation and Research (CBER); however, medical devices come under the jurisdiction of both CBER and the Center for Devices and Radiological Health. The product is cleared for use with bone graft materials to promote handling properties of the graft; however, the big market is for use as a “healing product” in other orthopedic settings.

Similarly, it is not at all clear who is authorized to collect, process and administer aPRP. In hospitals, procedures involving the collection and administration of a PRP are subject to medical staff credentialing. Outside the hospital, in an office or clinic setting, only state agencies and their practice of medicine regulations apply. Thus, anyone licensed by the state to practice or provide healthcare services might be able to use these devices/products, though they may have no knowledge of the collection and handling of blood and tissues for reinfusion purposes. Outside of those trained in transfusion medicine, most practitioners have little such knowledge or training, if any. Clinics and offices are not inspected, regulated nor audited compared to hospital activities and procedures.

Finally, who pays for this product? The Centers for Medicare and Medicaid Services have stated that a PRP will only be covered for treatment of chronic, non-healing diabetic, venous or pressure wounds if the patient is enrolled in a registered clinical trial. Application of the product to acute surgical wounds in the OR, orthopedic injuries in the clinic, and to the skin of “tired aging faces in the spa” are not covered. Thus, most patients are paying a lot for a treatment that has not demonstrated any improvement and outcome. The application of appropriate standards for the entirety of the collection and use of this product would be of great benefit to the public, as would careful clinical trials to see if it is actually effective, and in what circumstances


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