

# Toward a patient-based paradigm for blood transfusion

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**Abstract:** The current “manufacturing paradigm” of transfusion practice has detached transfusion from the clinical environment. As an example, fresh whole blood in large-volume hemorrhage may be superior to whole blood reconstituted from multiple components. Multicomponent apheresis can overcome logistical difficulties in matching patient needs with fresh component availability and can deliver the benefits of fresh whole blood. Because of the different transfusion needs of patients in emerging economies and the vulnerability of these blood systems to emerging infections, fresh whole blood and multicomponent apheresis can better meet patient needs when compared with transplants of the “manufacturing paradigm”. We propose that patient blood management, along with panels of repeat, paid, accredited apheresis and fresh whole-blood donors can be used in emerging economies to support decentralized blood services. This alternative transfusion–medicine paradigm could eventually also be adopted by established economies to focus transfusion medicine on local patient needs and to alleviate the problem of the aging volunteer donor base.

**Keywords:** indications, emerging countries, patient blood management

## Introduction – blood transfusion’s first paradigm

The inception of blood transfusion lies in the ancient recognition that acute blood loss can be fatal.<sup>1</sup> By World War I, developments in blood grouping and preservation allowed the establishment of the first “blood bank”.<sup>2</sup> This facilitated the logistics of blood delivery. Blood transfusion continued to develop over a succession of conflicts, stimulating the development of plasma fractionation and the introduction of blood bags.

If transfusion is seen as a series of paradigms,<sup>3</sup> the transfusion paradigm by the early 1960s involved the collection and transfusion of whole blood, with a focus on immunologic compatibility. In this “pre-evidence-based medicine” era, transfusion was primarily through whole blood and geared to assist surgery.

## The current transfusion paradigm in rich economies

Transfusion may be viewed as a series of paradigms, reflecting changes in technology and clinical practice.<sup>4,5</sup> We have previously suggested<sup>6</sup> (Figure 1) that the current transfusion paradigm is a “product” or “manufacturing” paradigm shaped by several determining factors.

## Inventory influence

Where blood systems have been delivered through governments, policies of national self-sufficiency in blood-derived therapies have been the norm. The treatment of

- Centralized blood systems
- Blood component therapy
- Manufacturing culture
- Focus on product
- Primacy of inventory
- Detachment from clinical environment

**Figure 1** Features of the current Western transfusion paradigm.

hemophilia A with plasma products drove these countries to increase blood collection with recovered plasma as the driver. In the US, a plasma industry separate from the blood collection sector ensured that plasma recovered as a by-product of whole blood collection was not a primary shaper of blood collection. Rather, the separation of plasma from red cells was influenced by the development of red cell additive solutions to increase red cell shelf life. In both systems, a primacy on output and inventory became a shaper of transfusion practice.

## Regulatory pressures

The blood sector in the rich economies is strongly regulated, primarily because of historical issues relating to blood-borne pathogens. This has contributed to quality management in transfusion activities, with attention focused on product rather than patient. The parameters used to qualify components for transfusion have limited relevance to their clinical efficacy, furthering the detachment of product characteristics from patient needs. Similar issues permeate proposals to extend platelet shelf life.

## Transfusion industry

Transfusion in 2013 has become the object of the medical subspecialty of “transfusion medicine”. It is a huge, multibillion dollar industry that delivers products in the developed countries through organizations which, in multisupplier systems such as in the US, compete vigorously for hospital blood needs.<sup>7</sup> The blood market in the US alone was estimated at \$9.5 billion in 2012.<sup>8</sup> Figure 2 summarizes our synthesis of the shapers of the current transfusion paradigm.

## Current paradigm – consequences and tensions

The evolution of transfusion medicine has strengthened greatly the transfusion industry, while contributing to a detachment from the clinical environment. Any research is well integrated into the current paradigm, and would be classified as “normal transfusion” in Kuhnian terms<sup>3</sup> (Figure 3),

- Blood providers
- Consumable providers
- Medical specialties
- Government bureaucracies
- Academic departments

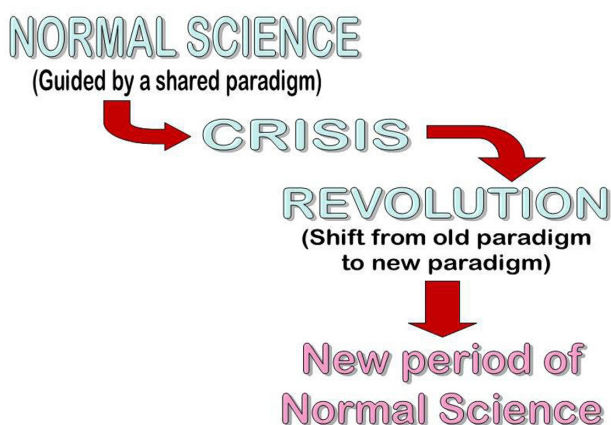
**Figure 2** Shapers of the current paradigm.

seldom questioning the tenets of the current paradigm until its replacement by a crisis. Several of these tenets (Figure 1) have converted “blood transfusion” to “stored blood component” transfusion.

The primary thrust of the “inventory” influence has been to maximize the resource through the practical logic of one donation serving many patients. The need to minimize transfusion-associated circulatory overload and transfusion-related acute lung injury (TRALI) is cited in support of the appropriateness of red cell versus whole blood transfusion. However, in massive transfusion, the inventory-driven argument regarding the appropriateness of “one donation–many patients” leads to exposure to many more donors than would occur when transfusing fresh whole blood. Additionally, evidence is lacking as to whether splitting blood donations into multiple components enhances inventory, or whether red cell delivery is physiologically optimal through transfusion of plasma-depleted additive-suspended erythrocytes.

## Outcomes in patients experiencing large blood loss

In obstetric hemorrhage<sup>9</sup> and trauma,<sup>10</sup> morbidity and mortality are improved when transfusing fresh whole blood rather than stored components or reconstituted whole



**Figure 3** The process of paradigm shift.

blood.<sup>11</sup> Transfusion requirements of patients with acute, severe hemorrhage are thus best met by fresh whole blood with a hemostatically intact profile. Three percent to 8% of trauma patients<sup>10</sup> and 2%–3% of patients with obstetric hemorrhage<sup>9</sup> qualify for fresh whole-blood transfusions, but require large amounts of blood, so that 15% of erythrocytes used in the US are for treating injury.<sup>12</sup> Like acute, severe hemorrhage, other indications for transfusion may be subject to similar revision of the most appropriate blood product. In cardiac surgery, for example, one unit of fresh whole blood has been reported to be hemostatically equivalent to six platelet units,<sup>13</sup> a finding which is likely linked to hemostatic properties additional to platelets, as survival in combat casualties did not differ between different platelet delivery methods.<sup>14</sup> Our understanding in this area is hampered by the lack of a definition of what constitutes “fresh blood”. We propose the definition used by the US Defense Medical Training Institute be considered.<sup>15</sup> A significant factor in the provision of fresh blood, as defined here, is the possible transmission of viral pathogens, which currently is minimized through screening tests, but may be logistically difficult to achieve in the prescribed time frame. In the military setting, where most of the experience regarding this area has accrued, the relative risk between screened and unscreened blood has been found to be insignificant when using accredited “walk-in” donors,<sup>16,17</sup> and is minimized further through rapid tests. As suggested by Spinella et al,<sup>16</sup> a comprehensive risk assessment comparing current infectious disease risks to the risk of using stored blood, rather than an unquestioned acceptance of historical concepts, is needed as an aid to decision making.

## Blood transfusion in surgery

Transfusion practice in similar established economies is highly variable,<sup>18</sup> lacks evidence,<sup>19</sup> and is independently associated with adverse events in cancer surgery,<sup>20</sup> cardiac surgery,<sup>21</sup> and noncardiac surgery;<sup>22</sup> although, causality as historically defined remains to be established in most settings.<sup>23</sup> The possible harm from stored erythrocytes has focused attention on the loss of nitric oxide during red cell storage,<sup>24</sup> leading to proposed new principles for the qualification of transfused erythrocytes, which have been met with reservations from the transfusion community.<sup>25</sup> This issue is currently being addressed in a number of randomized controlled trials,<sup>26</sup> and continues to yield controversial results.<sup>27</sup> Large prospective studies<sup>28</sup> and a recent meta-analysis,<sup>29</sup> combined with the demonstrated abnormalities of stored erythrocytes, should suffice to justify a precautionary approach such as has

underpinned much of transfusion practice in the past 20 years: based on a Popperian hypothesis, stored erythrocytes are harmful until shown not to be so. Such precautionary ideology continues to guide policy regarding infectious disease risks, which are in many environments, small compared to some of the estimated morbidities from stored red cells. Further specification of what constitutes “storage” in this issue would be helpful in assessing the data. We propose consideration of the large prospective study of Pettilä et al,<sup>28</sup> which allows a period of 8 days as the threshold above which red cells are stored with harmful effects on patients. This period is consistent to that found in the most recent review of studies detecting an effect associated with red cell storage period in critically ill patients.<sup>30</sup> While the issue is still under review, it may be prudent to direct inventory-driven efforts to continue to improve and prolong red cell storage and develop tools to optimize the available inventories.<sup>31</sup>

## Other components – platelets

Efforts continue to increase the supply of platelets through extending their shelf life. Recent years have seen the introduction of bacterial culture. The US Food and Drug Administration’s (FDA) Blood Products Advisory Committee has recommended that platelets also be subjected to a rapid release test after 4 days of storage,<sup>32</sup> while rejecting industry overtures to allow a shelf life of 7 days with a negative test. An inventory-driven approach to improving platelet logistics appears detached from product efficacy and safety matters given that the *in vivo* properties of platelets stored for 7 versus 5 days deteriorate significantly.<sup>33</sup> Clinical implications of platelet storage lesion have been reported from the trauma<sup>34</sup> and liver-transplant<sup>35</sup> settings.

Because of these risks, interventions aimed at reducing platelet transfusions have included reducing the threshold triggering prophylactic transfusion, administering low-dose platelet transfusions, and administering therapeutic (as opposed to prophylactic) platelet transfusions in specific clinical circumstances,<sup>36–39</sup> with due recognition for the need of further studies.<sup>40</sup> All these interventions deliver good outcomes if done in the context of intensive patient blood management (PBM).

The continued use of whole blood-derived platelets, which expose a patient to multiple donors to confer the same benefit as a single-donor unit (apheresis), also bears scrutiny. Apheresis platelets can reduce the risk of both transfusion-transmitted infections and TRALI.<sup>41,42</sup>

The resources currently focused on the maintenance of an inventory may, as with erythrocytes, be better allocated

to a more clinically focused strategy involving transfusion of fewer, fresher platelets. As in other areas, definitional problems underlie the concept of fresh platelets. We propose, for comparative purposes, the definition offered by the FDA, ie, platelets drawn, prepared, and transfused on the same day,<sup>43</sup> recognizing that practical considerations limit the capacity of any system to deliver such products, but wishing to accentuate the reality that platelet deterioration is progressive from the inception of storage.

## Fresh frozen plasma transfusion

Evidence for the use of fresh frozen plasma (FFP) is limited to the supplementation of stored components in massively transfused trauma victims<sup>44</sup> and thrombotic thrombocytopenic purpura.<sup>45</sup> Despite this, the widespread use of FFP continues through various poorly-evidenced guidelines. The assumed role of coagulation factors in thawed FFP has prompted studies on the quality of readily thawed refrigerated FFP, which is convenient logistically when addressing emergency transfusion.<sup>46</sup> This overlooks the additional vascular protective effects conferred by freshly-thawed FFP,<sup>47,48</sup> further exemplifying the product versus patient paradigm.

Plasma supplementation of massively-transfused patients was found to be unnecessary in a study conducted before the introduction of automated plasma removal<sup>49</sup> and depletion of the key protein, fibrinogen. FFP's role in massive transfusion may be addressed through the use of fresh whole blood instead of reconstituted whole blood from several donors. The repeated demonstration of lack of benefit from FFP transfusion should act as further incentive for more trials employing whole blood.

## Transfusion in emerging economies: is a transplant the best option?

For the purpose of this discussion we have classified countries as low income (LIC), middle income, and high income (HIC) as defined by the World Bank.<sup>50</sup> The World Health Organization (WHO) and donor agencies appear committed to instituting the Western paradigm as the route of choice in the emerging, resource-poor world, emphasizing the need for centralized blood systems, good-manufacturing-practice, and component therapy in sub-Saharan Africa.<sup>51</sup> A significant example is the US President's Emergency Plan for AIDS Relief.<sup>52</sup> These donor agencies must take into account qualitative differences in blood usage. The majority of recipients in emerging countries are younger and more likely to be women and children.<sup>53</sup> Transfusion most frequently occurs because of acute blood loss from injury and obstetric hemorrhage, which

are best treated with fresh whole blood, and for childhood anemia due to malaria.<sup>54</sup> The WHO recommends whole blood for malaria,<sup>55</sup> in which metabolic acidosis and hypovolemia<sup>56</sup> may be ameliorated by the fresh plasma portion.

The development of transfusion-associated circulatory overload in this patient demographic should not be presumed, because this transfusion complication occurs mostly in elderly patients.<sup>57</sup> Similarly, an increase in TRALI is not inevitable, since none was found in otherwise healthy battlefield casualties given whole blood,<sup>11</sup> while nonimmune mediated TRALI may be accentuated by stored components.<sup>58</sup>

The particular profile for blood use in these countries is reflective of their current economies. While we recognize the formidable problems which currently apply to transfusion practice in LIC,<sup>54,59</sup> we suggest that an opportunity may exist for the emerging world to bypass the western paradigm. The analogy with telephone systems, where the lack of landlines spurred the development and widespread provision of mobile phone technology, bears reflection.<sup>60</sup>

## A new paradigm – the patient first

PBM identifies a patient at risk for transfusion and formulates a multidisciplinary and multimodal, yet individualized, plan for reducing or eliminating the need for allogeneic transfusion. PBM integrates many hospital departments in a common effort to reduce allogeneic-donor exposures as much as possible, and thereby reduce both the infectious and immunologic risks of transfusion.<sup>61,62</sup> Its traction is currently exerted mainly with elective surgical procedures in the orthopedic, cardiac, and transplant areas, which occupy a high proportion of blood use in the rich but not in the emerging economies. PBM has led to sustained decreases in blood usage, with conflicting results in relation to conventional pharmacoeconomics, eg, in pharmacologic stimulation of red cell production.<sup>63,64</sup> Pharmacoeconomic analyses demonstrate the lack of conventionally measured cost-effectiveness of most of the blood safety measures in place in the developed world,<sup>65</sup> in contrast to many PBM interventions.<sup>66</sup> PBM has been embraced by the WHO,<sup>67</sup> and it presents an essential component of any emerging transfusion paradigm.

## Which products?

As discussed, the primary blood product which currently best satisfies the needs for most aspects of transfusion in LIC is fresh whole blood. The primary impediment to its provision is the qualification of the viral status of donations, which may be particularly impeded in small-throughput operations, as would ensue if collection is decentralized (see below).

This could be addressed through the formation of panels of repeat, accredited donors under contract, with a low risk profile assured through appropriate selection and testing, allowing for the use of blood not subject to long-term storage and preceding the completion of viral tests. Rapid testing technology may also be used.

The safety may also eventually be enhanced through pathogen reduction technology, which has been successfully employed to produce hemostatically intact whole blood and is currently under trial.<sup>68</sup> External programs for blood systems development in resource-poor economies should monitor the evolution of these emerging technologies.

As the profile of clinical need evolves, other needs will be encountered, including red cell concentrates for the alleviation of normovolemic anemia and platelets for hypoproliferative thrombocytopenia. Standardized protocols for these products and a quality system for their manufacture can be implemented within a hospital environment, without detaching the provision from the clinical interface. Gearing the production more closely to specific patient needs will transition these products from the manufacturing to the medical environment, detaching from mainstream pharmaceutical oversight to hospital accreditation. It will also allow specification of products to match more closely actual clinical needs, rather than antiquated and irrelevant requirements introduced into pharmacopeial type specifications, such as the current and largely irrelevant requirements of FFP and cryoprecipitate, which are specified for hemophilia A treatment. Continuing developments may modify the usage profile for these therapies, while continuing evidence of the storage lesion may make delivery of fresh products important. Further measures to increase safety may include minimizing donor exposures through the use of products obtained through multicomponent apheresis donations.<sup>42</sup>

Multicomponent-apheresis collection has enhanced capacity to provide inventory flexibility and sufficiency<sup>69</sup> through decentralized collection geared to specific patient needs, while also maximizing the availability of fresh cellular components.<sup>70</sup> We recognize that the current high cost of the relevant disposables is a concern, as is its dependence on a regular and reliable electric power supply. We propose that, as infrastructural improvement gains pace in LIC to resolve some of these issues, the cost-effectiveness of multicomponent-apheresis should be considered.<sup>71,72</sup> As the LIC evolve toward a transfusion demographic closer to that of HIC, with an aged transfused population of predominantly surgical patients<sup>73</sup> and a predictable requirement for cellular components for hematology–oncology patients, the establishment of

a multicomponent apheresis supply, along with the provision of fresh whole blood, would address all transfusion needs.

## Blood donation in a new paradigm

The blood donor base in the established economies is being diminished through demographic changes threatening the blood supply.<sup>74–76</sup> Concurrently, PBM has seen a decline in blood usage in several HIC environments.<sup>77</sup> The current donor population in these HIC environments comprises the “baby-boomer” and “generation X” groups,<sup>78</sup> which have different values compared to the “generation Y” and “generation Z” groups from which the donor base will have to be increasingly drawn. These values include those expected to be less conducive to volunteerism.<sup>79</sup>

The proposal of Tomasulo<sup>80</sup> to establish panels of committed paid professional donors to ensure safe donors focused on patient outcomes merits consideration. Such a system based on strict contractual arrangements between donor and blood agency may conform better to safety and quality principles. The nonusage of the first donation may be considered, analogous to that applied for paid plasma donors.<sup>81</sup> Recalling that apheresis collection may be central to a new paradigm,<sup>42</sup> and that the experience of the plasma industry demonstrates that plasmapheresis donors require payment,<sup>82</sup> an approach incorporating committed paid apheresis donors may contribute to addressing the problems emerging from the demographic changes outlined above. The experience of plasma collection has shown that the required commitment to regular apheresis cannot be met through unpaid donors, and donor payment is compatible with a safe and regular supply,<sup>83–85</sup> although we emphasize that is not an essential feature of a new paradigm as long as patient needs are met. The construction of a panel of committed, healthy repeat donors for the provision of a whole-blood and apheresis-based supply requires more attention devoted to matching donor availability to the clinical needs of patients than has been possible in the operation of traditional blood agencies. The provision of free, long-term medical treatment for mainstream blood donors by the Malaysian blood service, which is a strong supporter of the WHO-sponsored unpaid donor policy, may bear consideration.<sup>86</sup> This approach can also form the basis for a new donor recruitment/retention paradigm for apheresis donors. The cost-effectiveness and long-term viability of such a system should be analyzed relative to the current paradigm, and a multifaceted system may be geared to specific patient demographics and needs.

“Catch-all” blood drives driven by inventory considerations rarely generate more than an average of two donations per donor annually. An apheresis-based system can be carefully geared to a planned clinical transfusion program as is possible for much of elective surgery and many medical indications, more appropriately matching to clinical needs as is already done through the provision of human leukocyte antigen-matched apheresis platelets.

## The blood center in the new paradigm

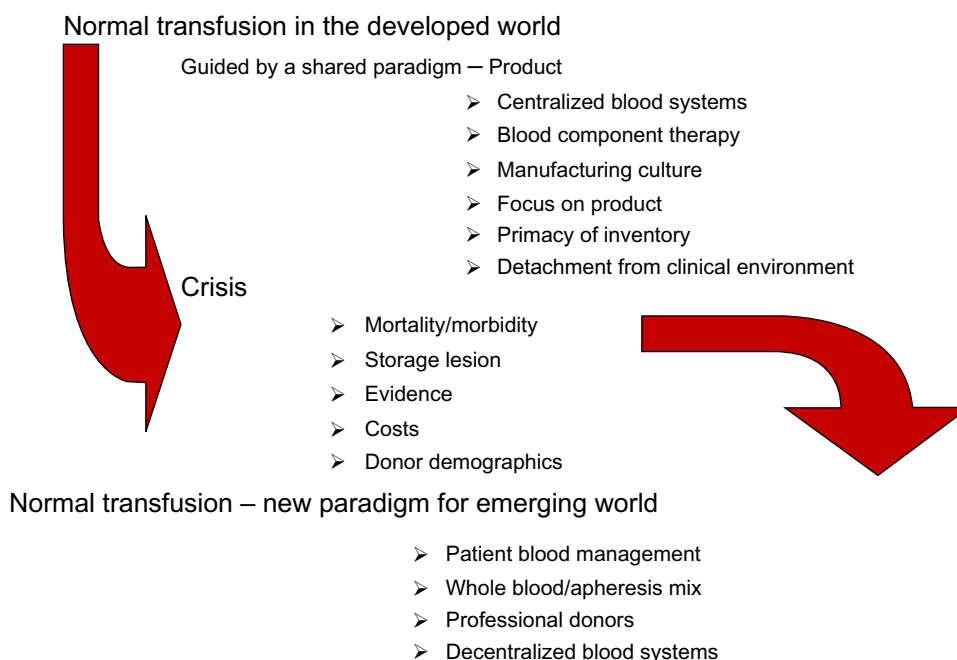
In HIC, centralized blood collection and processing centers supplying to remote clinical units are the predominant transfusion system. There are merits in both centralized and decentralized systems in these countries.<sup>87,88</sup> In LIC such as sub-Saharan Africa, centralized systems initially introduced by the colonial powers were replaced by decentralized services delivering good transfusion outcomes at lower costs.<sup>89–91</sup> Subsequently, economic pressures leading to the need for external aid have resulted in a surge toward centralizing blood systems as a condition of such aid.<sup>51</sup> This pressure is often premised on the minimization of human immunodeficiency virus and other infectious disease transmission through such centralization. There is no evidence that centralization in blood services reduced transfusion-transmitted acquired immunodeficiency syndrome, or that it impeded the penetration of West Nile virus and variant Creutzfeldt-Jakob disease in more recent times. The global

transfusion landscape continues to be vulnerable to the threat of infectious diseases. Any benefits from centralization are therefore detached from the issue of blood safety. The possible benefits need to be weighed against the increased costs and, in particular, to the inevitable detachment of blood service from patient care, which is a feature of most HIC systems.

The maintenance of adequate inventories must be more inventively geared to patient needs. Expertise in linear programming will assist blood centers to optimize allocation.<sup>92</sup> Similarly, a multidisciplinary effort involving the whole range of stakeholders in platelet delivery can reduce outdate ratios as well as decrease platelet shelf life,<sup>93</sup> while integrating patient history and engaging knowledgeable staff can limit platelet outdating to 1% of inventory.<sup>94</sup>

Such techniques will enable inventory management to become subservient to clinical need, rather than, as in the current paradigm, threatening to allow inventory management to dominate and determine clinical need.

The ongoing debate regarding the possible association of mortality and morbidity may require novel approaches linking red cell shelf life to patient category, allowing the limitation of shelf life to 7 days for the penalty of a 3.2% increase in the outdate rate.<sup>95</sup> Efforts to introduce these kinds of measures depend entirely on the closer integration of blood delivery and clinical areas, which is difficult to achieve through remote blood centers.



**Figure 4** Evolution of a new transfusion paradigm.

## Conclusion

Our purpose in this work was to show how much of what is regarded as infallible dogma in the mainstream transfusion medicine community rests on limited empirical evidence. We have developed concepts in parallel, that have been published elsewhere,<sup>6,42</sup> on the application of the thinking of Kuhn and Popper to the field of transfusion medicine. We believe that the concepts we have further developed here may prove useful in understanding the current state of our field and its contribution to patient care in emerging economies. We propose the development of a new transfusion paradigm for the emerging world and its eventual adoption by the rich economies through a process of Kuhnian revolution (Figure 4). A feature of such a process is the incommensurability between successive paradigms. While the enhanced appreciation of product quality and standardized manufacture of the current paradigm are desirable and retainable features, the detachment from patient-centeredness renders the transition to the new paradigm as dramatic as Kuhn described.<sup>96</sup> As patient-centeredness becomes more important in health care, our field should be foremost in adopting its principles.

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## Disclosure

The authors report no conflicts of interest in this work.

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