Towards the future of blood transfusion – the South African National Blood Service's perspectives on cellular therapeutic services and products

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Blood transfusion services are the cornerstone of the healthcare delivery system, and need to stay abreast of advances in technology to ensure relevance to the needs of the country. In this review, we examine the current status of blood transfusion systems and discuss their possible future role in cellular therapies.

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South Africa (SA) is challenged with a quadruple burden of disease that reflects the complex nature of its population and healthcare delivery systems. These diseases include maternal, new-born and child health; HIV/AIDS and tuberculosis (TB); non-communicable diseases; and violence and trauma.[1] The management of most of these diseases includes, at least in part, the use of blood and blood products, while future management will increasingly involve novel cellular therapeutic services and products.

The primary objective of blood transfusion services in SA is to supply safe, sufficient, quality blood products in an equitable manner to all patients in need. This mandate is met by the South African National Blood Service (SANBS), which supplies products to 8 of the 9 provinces, and the Western Cape Blood Service (WCBS), which supplies blood products to Western Cape Province.

In 2018, SANBS provided more than a million blood products to more than 320 000 patients. SANBS has actively increased the size of the black donor panel (Fig. 1) as well as the number of units collected from these donors (Fig. 2). The main drivers of blood product use in SA include obstetric haemorrhage, treatment of a multitude of cytopaenias associated with diseases such as HIV,[2] TB and other medical conditions, and trauma and surgical emergencies (Table 1). This is in contrast to developed countries where most blood components are issued to elderly

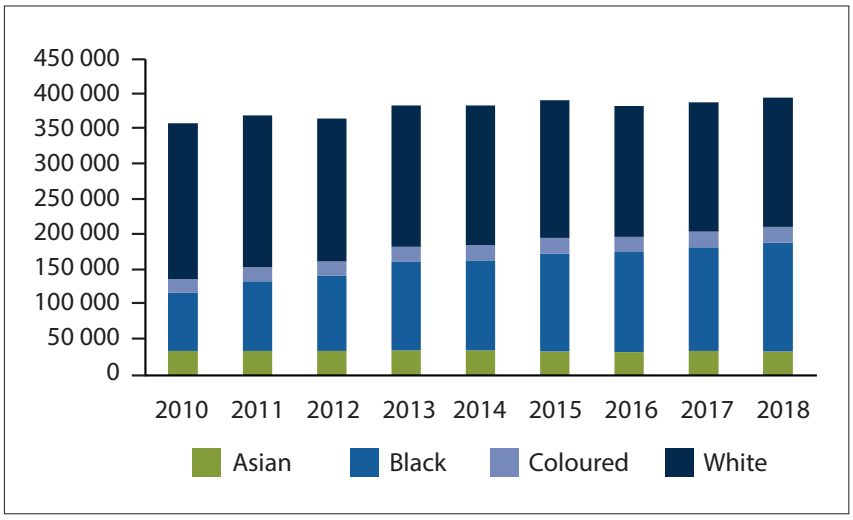

Fig. 1. Distribution of active donor panel by ethnic group from 2010 to 2018.

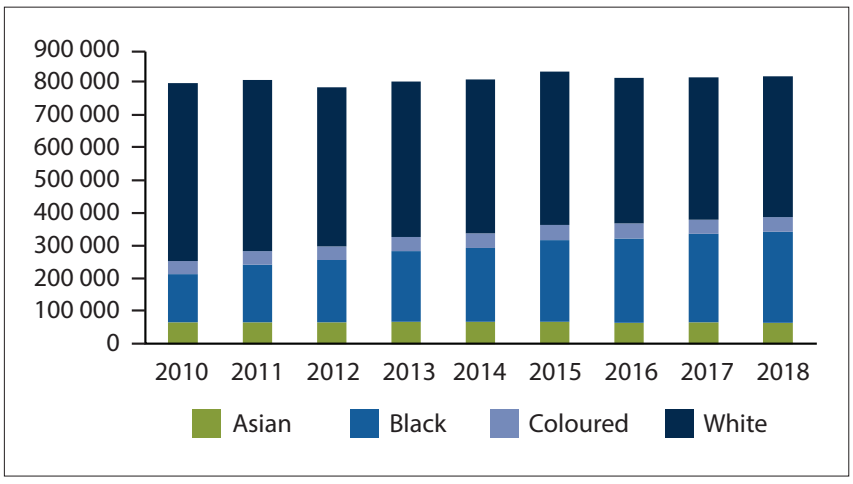

Fig. 2. Distribution of successful collections by ethnic group from 2010 to 2018.

patients undergoing complex cardiovascular and orthopaedic surgery, those who have trauma or sepsis, and patients who require supportive therapy while being treated for malignancies.[3]

To meet the needs of these patients, the healthcare system requires a constant supply of safe blood products. Donation of blood in SA is on a voluntary, non-remunerated basis, therefore the blood supply is precarious and relies on the willingness of healthy people to donate regularly.

Currently, up to 20% of the SA donor population is deferred for various reasons, including various medical conditions and surgical interventions, exposures and behaviours placing potential donors at risk of transfusion transmissible infections as well as travel to malaria endemic areas (Table 2). However, the single biggest reason for deferral, accounting for almost 50% of deferrals, is donors presenting with low haemoglobin levels.[4] Ensuring a sufficient blood supply while maintaining donor health in general (and iron levels in particular) remains an ongoing challenge, especially in a country where the blood demand is increasing as access to healthcare in previously disadvantaged communities improves. In this review, we consider the current landscape and the future direction of this paradigm shift in SANBS.

Table 1. Number of products issued by discipline during 2018

Discipline	Products issued, *n (%)*
Burn units	3 834 (0.4)
Cardiothoracic surgery	23 762 (2.3)
General surgery	115 841 (11.3)
Obstetrics and gynaecology	173 087 (16.9)
Haematology/oncology	62 196 (6.1)
ICU	171 088 (16.7)
Infectious diseases	1 651 (0.2)
Medical	296 157 (28.9)
Orthopaedics	23 044 (2.2)
Other	30 055 (2.9)
Paediatric surgery	2 428 (0.2)
Paediatrics	46 842 (4.6)
Trauma	28 610 (2.8)
Unknown	45 599 (4.5)
Total, *N*	1 024 194

Table 2. Distribution of donor deferrals, 2018

Deferral type	Deferrals 2018, *n* (%)
Haematocrit/haemoglobin	93 215 (43.2)
High-risk exposures	33 976 (15.8)
Malaria risk	5 269 (2.4)
Medical conditions/medication	60 785 (28.2)
Pregnancy	7 077 (3.3)
Surgery/trauma	14 196 (6.6)
Weight	1 039 (0.5)
Total, *N*	215 557

The current landscape

Patient blood management

In response to both an increasing demand for blood products in developing countries and concerns regarding potential over-transfusion of patients in developed countries, the World Health Assembly recommended the implementation of patient blood management (PBM) to its member states in 2010.[5] PBM is an evidence-based bundle of care that optimises medical and surgical patient outcomes by clinically managing and preserving a patient's blood.[6]

The three pillars of PBM address anaemia, bleeding and preserving the patient's own blood. A programmatic approach to PBM has been associated with improved patient and economic outcomes and reduced transfusion rates.[6] Successful national adoption of PBM in SA will assist in addressing concerns around liberal transfusion practices in certain sectors of the healthcare system, while at the same time increasing availability of products in historically underserviced areas, such as district hospitals in deep rural areas.

Internationally, the underlying rationale for this patient-centric approach is simple and compelling: PBM is not only associated with better patient outcomes, but also with a reduction in healthcare expenditure.[6-8]

Consequently, the implementation of PBM is becoming more widespread and, where this occurs, blood transfusion services – especially in developed countries – are experiencing a significant decline in blood use.[9] In addition, new developments in the management of many diseases have created demand for new blood products and services. In response to this changing landscape, blood transfusion services are expanding their service and product offering, which may include therapeutic apheresis and cellular therapies.[10]

As we continue implementing PBM in the diverse and complex South African healthcare environment, our focus shifts from product to patient. This patient focus includes therapeutic apheresis and cellular therapies.

Therapeutic apheresis services

Therapeutic apheresis is a treatment modality that involves drawing a patient's blood, separating and removing a targeted component, and retransfusing the remainder of the blood components into thepatient. Current evidence recommends it as part of first- or second-line treatment for a host of immunological disorders.[11]

SANBS has provided therapeutic apheresis services in the form of plasma exchange, leucopheresis, red cell exchange and haematopoietic progenitor stem cell collections since 1997.

The most common indication for therapeutic apheresis is plasma exchange for thrombotic thrombocytopenic purpura (TTP) in HIV-positive patients.[12] TTP is a medical emergency that presents with a thrombotic microangiopathy and is associated with a 90% mortality rate if untreated.[13,14] From 2011 to 2018, SANBS performed 5 267 plasma exchange procedures on 517 patients with TTP in 21 hospitals. Most of these patients were HIV-positive (78%) and antiretroviral naive at the time of diagnosis. Two recent publications on the survival rate of TTP patients with HIV in South Africa treated with plasma exchange report survival rates of 70.7% and 96.5% respectively.[15,16] TTP may provide unique research opportunities into the effect of HIV on vascular biology generally, and on the endothelium specifically, through ADAMTS13 and Von Willebrand Factor (VWF) testing,[14] as well as next-generation sequencing, transcriptomics and proteomics.

Other less common indications for plasma exchange referred to SANBS include neuromyelitis optica, acute inflammatory demyelinating polyneuropathy, myasthenia gravis including myasthenic crisis, and antibody-mediated renal transplant rejection.

Cellular therapy services

Haematopoietic stem cell transplantation (HSCT) is a procedure where stem cells are collected from an autologous or allogeneic

donor, processed and, if required, stored. After the patient receives a conditioning regimen, which may include radiation or high-dose chemotherapy, the processed cells are returned via intravenous infusion to regenerate the injured bone marrow. This procedure is often lifesaving and performed mainly on patients suffering from haematological malignancies and bone marrow failure syndromes.[17] The services which SANBS provides for HSCT patients include haematopoietic stem cell collection by apheresis, cryopreservation and thawing of collected cells, and $CD34^+$ enumeration by flow cytometry.

A review by Baldomero *et al.*[18] reported significant gaps in HSCT rates in the World Health Organization's combined Eastern Mediterranean and African region. They noted that only 29 (or 1.85%) of transplant teams globally were operating in this region, performing 2 332 (3.3%) of the 71 036 HSCTs performed worldwide between 2006 and 2013.[18] Although this figure represents a 90% increase in the number of procedures from 2006 to 2013, this remains the region with the lowest transplant rates.

In SA, much has changed since 2013: new centres in both the public and private sectors have opened in Bloemfontein, Port Elizabeth, Umhlanga and Polokwane. Alberts Cellular Therapy (ACT) in Pretoria became the first unit in Africa to obtain international accreditation. In addition, haplo-identical transplant programmes were started successfully at both ACT and Groote Schuur Hospital in Cape Town, which significantly increase access to donors, even though most of the centres do not provide comprehensive stem cell transplantation programmes.

From January 2013 to July 2018, 546 patients were referred to SANBS for haematopoietic stem cell apheresis (HPC-A) from 13 hospitals in both the public and private sectors across 4 provinces (Gauteng, Free State, KwaZulu-Natal and Eastern Cape) (Table 3). The most common procedure performed was autologous transplantation (*n*=491/546; 89.9%) and the most common indication was multiple myeloma. To date, very few allogeneic stem cell transplants have been performed by the units supported by SANBS.

To date, the number of patients referred and the number of units referring patients to SANBS continues to grow annually, reflecting the growing SANBS footprint, and also the expansion of access to such services by an increasing proportion of the population.

SANBS has developed HSCT service capacity in a similar fashion to other national or regional blood transfusion services, such as Sanquin in the Netherlands, and, once accreditation by the Joint Accreditation Committee of the International Society for Cellular Therapy and the European Society for Blood and Marrow Transplantation (JACIE) is obtained in 2020, SANBS will match its peers internationally.

Translational research

Blood transfusion services need to constantly balance the country's current need for a safe, sustainable and cost-efficient blood supply against the need to develop specialised services and products that will be required in the future to support new therapeutic interventions. Transfusion and cellular-related translational research has been at the forefront of balancing these sometimes competing needs.[19]

Table 3. Number of transplant units accessing the SANBS cellular therapy services, 2013 - 2017

Heathcare setting	2013	2014	2015	2016	2017
Public	3	2	4	6	6
Private	5	5	5	7	6
Total	8	7	9	13	12

SANBS = South African National Blood Service.

In SA, the implementation of individual donation nucleic acid amplification testing for HIV, hepatitis B (HBV) and hepatitis C (HCV) significantly altered blood collection practices, while simultaneously improving the safety of the country's blood supply to be comparable to that of many developed countries.[20,21]

Similarly, advances in monoclonal antibody-based blood group serology and, more recently, molecular DNA-based blood group testing, have improved compatibility testing in general and, particularly, in obstetric and prenatal medicine. This technique is used to differentiate between certain D antigens, such as weak D and partial D subgroups, which determine the need for Rh-immune prophylaxis to minimise the risk of haemolytic disease of the fetus and newborn.[22]

New technologies, such as pathogen reduction (PR) treatment of platelets introduced in several developed countries, will address bacterial contamination – as well as emerging infectious risks – up to now the most common adverse events associated with platelet transfusion.[23] Implementation of PR technology in SA in future may help alleviate chronic platelet shortages by enabling the use of relatively more plentiful buffy-coat-derived platelet products for many indications where single-donor apheresis platelet products are currently recommended.

A less appreciated area is the role that blood transfusion services play in ongoing HIV cure research. The Fiebig stage classification of the HIV immune response was developed through the analysis of stored blood products of repeat blood donors who tested HIV-positive on subsequent donations.[24]

This cutting-edge basis of molecular testing for HIV is currently being further refined through the development of assays to quantify replication-competent, non-induced proviruses in the latent reservoir in fully suppressed HIV-positive patients.[25] SANBS is actively involved in local HIV research through the National Heart, Lung and Blood Institute-funded REDS-III Management and Acute Treatment of HIV Study (MATHS).[26] This study enrolled 41 participants with acute HIV infection and 28 participants with recently acquired HIV, initiated very early antiretroviral treatment (ART) and followed the participants' progress for up to 3 years. The main aims of the study were to establish the size of the peripheral blood viral reservoir at initiation of ART and at defined time points during follow-up, and to conduct a 'proof of concept' study to show how blood donors identified as having acute HIV infection and recently acquired HIV infection can be successfully linked to care and enrolled in a follow-up study with a national footprint.

New but rapidly expanding fields in international transfusion and cellular translational research focus on the production of cell lineages for use in a multitude of settings. Of potential critical importance to blood transfusion is the production of functional mature red blood cells from embryonic stem cells.[27]

Future direction

Cellular therapies provide an alternative and/or adjunct treatment to bridge the current unmet clinical demand in a range of chronic disorders, from non-communicable diseases, such as diabetes, to infectious diseases, including TB and HIV, and a multitude of malignancies. Here, we highlight a number of these promising therapeutic possibilities. SANBS will continue to investigate the feasibility of providing these products, or at least determine how best to support services associated with them.

Mesenchymal stromal cells

Mesenchymal stromal cells (MSCs) represent a population of tissue-resident non-haematopoietic adult progenitor cells originally

identified in bone marrow and subsequently in a number of organs, including adipose tissue.[28]

These cells can easily be expanded from adipose tissue as they can be grown in tissue culture and have the capacity to differentiate into fat, cartilage and bone. When reinfused, they are believed to migrate to sites of injury and inflammation, promoting tissue repair. Numerous clinical trials are ongoing in bone and cartilage repair and other settings.[29]

MSCs have other unique qualities. Recent studies have shown significantly reduced insulin requirement in patients with type I diabetes after the administration of Wharton's jelly-derived (umbilical-cord) MSCs.[30] Similar results were shown in an open-label clinical trial after co-transplantation of adipose-derived MSCs and haematopoietic stem cells in the same population. In addition, MSCs dampen inflammation through an array of interactions with innate and adaptive immune cells, thereby modulating immune responses.[31]

An ongoing study in Durban, SA, is establishing the safety of adjuvant autologous MSC therapy in SA patients with multidrug-resistant or extreme multidrug-resistant TB. These patients, in particular, would benefit from immune modulation to prevent the tissue damage caused by the immune response to the TB microbe.[32] These are all promising research areas and SANBS is exploring the commercial production of MSCs and testing in clinical trials.

Natural killer cells

Natural killer (NK) cells play a critical role in viral immunity. In the HIV infection setting, epidemiological and functional evidence supports a role for NK cells in both protection from infection acquisition as well as in viral control.[33]

NK cells directly mediate immune pressure leading to virus evolution, and NK cell receptor genotypic profiles, clonal repertoires and functional capacity have all been implicated in virus containment. In addition, indirect NK cell-mediated antibody-dependent cellular cytotoxicity has been linked to vaccine-induced protective immunity against HIV infection.

With recent advances in the understanding of NK cell deficiency, development, memory-like responses and editing of the adaptive immune system, the opportunities to direct and exploit NK cell antiviral immunity to target HIV have grown exponentially.[34] To this point, a recent publication on a SA cohort study by Ramsuran *et al*.[35] confirms the hypothesis that NK cell function is linked to HLA-A overexpression, which may lead to rapid progression in a subset of HIV-positive patients in SA.[35]

One possibility to address NK cell dysfunction will be to transfer NK cells with different functionality from genotypically different donors, an example of adoptive immunotherapy in the treatment of HIV. SANBS endeavours to collaborate with other researchers in this field to create the pathway for the delivery of potential adoptive therapies to the patient.

Chimeric antigen receptor T cells

The various eras of treatment of malignancies are marked by increasing tumour specificity. In 2018, the first chimeric antigen receptor T cell (CART) products (axicabtagene ciloleucel and tisagenlecleucel) were approved for clinical use, heralding the dawn of immune therapies for certain B cell leukaemias and lymphomas.[36]

Chimeric antigen receptors are receptor proteins that have been engineered to give T cells a new ability to target a tumour neoantigen. The chimeric nature of these receptors stems from the combined antigen-binding and T cell-activating functions in a single receptor. These genetically modified cytotoxic T cells have the ability to target not only tumour cells, but also cells infected by viruses. Consequently, the first T cells against HIV infection have already been produced and are being tested in clinical trials.[37]

This field is rapidly expanding: by October 2018, 322 'chimeric antigen receptor' clinical trials (128 recruiting in the USA and 158 in China) were registered on clinicaltrials.gov, covering a range of indications, including haematological malignancies, solid-organ tumours, and autoimmune and infectious diseases.

These data are compared to fewer than 10 such trials registered in September 2010, 77 in September 2015, and 144 in September 2016. The probability of breakthrough treatments for targeted diseases has increased significantly, and the SA healthcare system will have to prepare for this new treatment modality. SANBS can play a critical role in the harvesting, production and quality assurance of CART cells, and aims to collaborate with and assist the South African Stem Cell Transplantation Society with future platforms to ensure the SA public has access to such therapies.

Production of red blood cells

Recent advances in stem cell culturing techniques have seen an increase in approaches aimed at manufacturing red blood cells and platelets *ex vivo*. In SA, this development will address the risk of decreasing blood donor pools compounded by an ageing donor population and a growing national blood demand, as well as blood safety issues posed by the current HIV epidemic and emerging pathogens, all of which are predicted to be a threat to blood supply in SA.[27]

The UK's National Health Service has been one of the first services to take up the challenge to produce red cell products grown *ex vivo*. Although there are infrastructural, technological and financial challenges, these will most likely be overcome as technology becomes faster, better and cheaper, making the production of blood products *ex vivo* in a financially sustainable manner feasible in the medium term.

Next steps

When one considers the history of blood services, from the first transfusion of non-tested blood products in 1 625 to the quality and blood safety standards of today, it is no surprise that blood services are at the forefront of implementing new technologies and products to improve patient outcomes. New technologies aimed at producing MSCs, NK cells and CART cell products show real promise, and should be pursued as a new pillar of therapeutic options to alleviate the burden of disease in SA. SANBS aims to contribute to this field in a step-by-step manner.

Firstly, we are focused on obtaining an appropriate international accreditation standard (JACIE) by 2020. Secondly, we will establish a translational research office in collaboration with our local and international experts, with a clearly defined research agenda that includes novel therapies and products. Thirdly, we will establish a production plant which will produce products such as human platelet lysate (a stem-cell growth medium) and MSCs, as the forerunners of more advanced cell products.

Finally, SANBS will also work towards meeting advanced therapy medicinal products (ATMP) standards and regulatory approval. The *Official Journal of the European Union* defines ATMP as either one or a combination of gene-therapy medicinal products, somatic cell therapy medicinal products or tissue-engineered products.[38]

The proposed South African National Health Insurance Bill necessitates the careful consideration and appropriate use of both health products and services with a clear focus on sustainability within the resource-constrained environment of the SA healthcare

environment. Ongoing research suggests that access to curative procedures and products may be cost effective when it increases the probability of cure and reduces the need for further lines of therapy. This dynamic is seen when performing an allogeneic stem cell transplant early in the course of high-risk leukaemia and may be proven in cellular therapies such as CART cells in B-acute lymphoblastic leukaemia.[39] Towards this end, SANBS will continue to support best-practice, evidence-based transfusion services and pursue close collaboration with bodies such as the South African Centre for Epidemiological Modelling and Analysis, the South African Health Products Regulatory Authority, and the Department of Health to ensure improved population-based health outcomes and sustainability.

Conclusion

As we consider the future of blood transfusion, it is evident that PBM and rapid changes in the management of diseases will force services to reinvent themselves. SANBS will do so by expanding into the field of therapeutic apheresis and cellular therapies in order to offer a much-needed new therapeutic pillar that may offer cures for many who suffer from infectious and malignant diseases.

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