Study limitations
With regard to the limitations of this survey, a key issue is the extent to which our findings can be generalised to all patients seen by private general practitioners in the Cape Peninsula and Stellenbosch. The geographical distribution of sentinel practitioners within the catchment area can be considered adequate to provide a patient sample of varying socio-economic status. However, participating general practitioners differed from a randomly selected group in a number of ways. They were more likely to be young, female, qualified in family practice and in solo practice. A similar trend was found in the Ambulatory Sentinel Practice Network of North America (ASPAN). The under-representation of graduates from Afrikaans-language universities can be attributed to the fact that SASPREN doctors were recruited mainly from the membership list of the Academy of Family Practice, which enjoys stronger support among English-speaking general practitioners.

The network should attempt to obtain a more representative sample of practitioners in the future. Whether complete representativeness is achievable remains doubtful, as doctors who voluntarily participate in research tend to be atypical and this constitutes a potential source of bias. Current evidence does not, however, enable us to determine with any certainty whether the above differences have influenced the results of this study. Future research should explore this possibility.

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National strategy for the prevention and management of transfusion-associated hepatitis


Statement of purpose
The screening of potential blood donors for the hepatitis B (HBV) and C (HCV) viruses has decreased the risk of transfusion-associated hepatitis. There remains, however, a lack of consensus on a number of issues including methods for screening of blood donors and the management of donors found to have markers of hepatitis virus infection. This document outlines the recommendations of a large group of interested individuals including blood transfusion service managers, primary care health authorities, epidemiologists, virologists, pathologists, gastro-enterologists and hepatologists drawn from both the public and the private sector.

Introduction
The incidence of transfusion-associated hepatitis (TAH) has declined significantly over the past decade. This is largely the result of stringent clinical screening procedures; improvements in detection of the hepatitis viruses; and advances in the treatment of pooled plasma products. The true incidence of TAH in South Africa is not known. In the USA only 5 - 10% of cases of TAH are reported to the transfusion services, and there is wide disparity in its prevalence determined by active versus passive surveillance.

Five hepatotropic viruses, A, B, C, D and E, are well characterised. A sixth virus, hepatitis G, has been partially characterised and other poorly characterised forms, currently termed non-B, non-C (NBNC), have been shown to exist. All of the well-characterised agents, with the possible exception of hepatitis E, may cause TAH.

South African blood transfusion services exclude donors at risk for hepatitis and screen all units, as well as plasma used in the manufacture of coagulation factor concentrates and immunoglobulin products, for hepatitis B and C.

Screening procedures must be highly sensitive, to avoid transmitting disease to recipients, and specific, to avoid depleting the donor pool. However, procedures must also be cost-effective and a balance has to be found between the cost of the increasingly sophisticated and expensive tests, the diminishing return of these tests, and the health impact and potential litigation associated with not performing additional screening tests.

With the exception of hepatitis B, all common hepatotropic viruses contain single-strand RNA (ssRNA). HAV, HCV and HEV contain positive-sense RNA, i.e.
following entry into the cell, the viral RNA serves as messenger RNA and uses the cellular machinery to form its proteins. These viruses all have a linear genome, which is translated into a single polyprotein which is then cleaved to form the various viral proteins. HDV, an incomplete virus which can only exist in the presence of HBV, is very rarely found in South Africa, and its transmission will be prevented by strategies to prevent transmission of HBV. HDV is a partially characterised positive-sense single-stranded RNA virus with approximately 26% amino-acid homology with HCV. It may cause mild acute or a low-grade chronic hepatitis, and is thought to be the main cause of NBNC TAH. It has been found in 1.7% of 1 478 blood donors in the USA, but no data are available in South Africa. Antibody assays are not yet available.

Hepatitis B
A partially double-stranded DNA virus is a member of the Hepadnaviridae family. It consists of a surface coat (HBsAg) and a core particle, the latter containing viral DNA, DNA polymerase and the core antigen (HBCAg). The viral DNA codes for four major polypeptides: the envelope, the nucleocapsid (core), the DNA polymerase, and the 'X' product. Mutations may result in altered or absent products. These may influence the pathogenicity of the virus or affect immune recognition and hence the ability of serological tests to detect the virus. A number of HBV variants have been described. It is not known whether these variants are important in South African TAH. However, variants may become more important with the advent of vaccination.

Screening for hepatitis B
The presence of HBsAg is the single most important screening test for the detection of hepatitis B. Both radio-immunoassays (RIA) and enzyme-linked immunoassays (EIA) are used for the detection of HBsAg and have a detection limit of 0.02-1 ng/ml. Both of these highly specific, sensitive and cost-effective methods will screen out the vast majority of hepatitis B-infected individuals. In a small number of cases HBsAg may be absent in patients with hepatitis B. This occurs in subjects in the 'window phase' of the acute infection and those with variant viruses. Although screening of donors for aminotransferases may detect some of these subjects, these tests are nonspecific, insensitive, costly and may result in a depleted donor pool. In the USA a recent survey of 15.4 million blood/blood product transfusions in the USA revealed 1 263 cases of TAH. Forty-four per cent of these were caused by HBV. In addition, 8 cases of fulminant hepatitis B in transfusion recipients of HBsAg-negative blood have been described. These were associated with mutant viruses.

The prevalence of HBsAg-negative but HBV-DNA-positive cases in the South African donor population is unknown. Prospective studies have shown that HBV-DNA is present in 4% of HBsAg-negative donors in Taiwan. The high prevalence and early age of acquisition of HBV in South Africa suggest that a similar prevalence of HBsAg-negative variants may be present here. Clues to HBV-DNA in HBsAg-negative cases include the presence of high-titre Hbc antibodies, which may be the only marker of hepatitis B.

Unfortunately, Hbc antibodies do not appear to be predictive of HBV infectivity. In South Africa, results of various HBV seroprevalence studies on asymptomatic individuals indicate that anti-Hbc, as a sole marker, is present in 4.5% of individuals. Preliminary data from two cohorts tested to date indicate that HBV-DNA is not present in these samples (S. Aspinall — personal communication).

Recommendations
All blood donations must be screened for HBsAg. Further studies are needed to resolve the worldwide controversy on the need to screen for anti-Hbc. A local prospective study of the incidence of TAH, and of the prevalence of hepatitis B variant viruses in the donor population, is required. Subjects who are HBsAg-positive should be referred to a physician with a special interest in hepatitis for counselling, management and follow-up.

Management
Donors positive for hepatitis B should be referred to a physician with a special interest in hepatitis. Subsequent management will include diagnosing the nature (acute or chronic), and complications (e.g. cirrhosis) of the HBV infection; notifying the subject to the public health authorities; immunisation of household and sexual contacts, education of the affected person; and where appropriate treatment of the disease (see below).

Hepatitis C
Hepatitis C is a positive-sense, single-stranded RNA virus related to the Pestiviridae and Flaviviridae. At least nine major genotypes have been identified, with associated variations in pathogenicity and biological behaviour. The virus causes chronic disease in the majority of infected subjects and as such may have an enormous medical and economic impact on the individual and on the health services. Before introduction of specific screening of blood products, HCV was the major cause of TAH in the USA, accounting for more than 90% of cases in prospective surveys. The proportion of NANB hepatitis associated with transfusion dropped from 16% in 1982 to 5% in 1990 in the USA with testing for surrogate markers and more careful donor selection.

Screening for HCV
Most South African transfusion services currently use third-generation assays to screen blood for HCV antibodies. These incorporate recombinant antigens and/or synthetic peptides derived from core, NS3 and NS4 regions, plus a recombinant protein derived from the NSS region.

The prevalence of HCV antibodies detected by the Abbott second-generation EIA in 66 314 donors studied at the Western Province Blood Transfusion Service was 0.41%. PCR was positive in only 13.6% of 184 of these subjects who had further testing. The prevalence of PCR-positive cases in the donor population was thus only 0.05%. In addition, only 75 of 184 cases that were antibody-positive
using the Abbott assay were also positive for antibodies to HCV by the Ortho EIA. All 25 PCR-positive cases were antibody-positive using the Ortho assay, while in the 159 PCRNegative donors, 50 were positive by the Ortho EIA, 107 negative and 2 indeterminate. Other studies using recombinant immunoblot assays to 4 HCV proteins (4-RIBA), have also shown a relatively poor correlation between second- and third-generation antibody assays and the presence of HCV RNA.

Genotyping of the PCR-positive fragments revealed that 20% were genotype 1, 8% were type 2, 12% type 3, none type 4 and 28% type 5, while the genotype of 12% was impossible to determine.

From this it is clear that HCV has a very low prevalence in the Western Cape and that the predictive value for virusemia of a positive test is low. Persistently positive anti-HCV persons remain excluded from the donor pool irrespective of PCR status.

**Recommendations**

All donations should be screened for HCV antibodies using second- or third-generation assays. Positive donors should be removed from the donor pool. Positive persons should be referred to a physician with a special interest in hepatitis. Subjects who test positive by PCR and have raised aminotransferase levels should undergo liver biopsy to assess disease activity and be treated if they meet the criteria detailed below.

### Hepatitis A

HAV, a non-enveloped, positive-sense, single-stranded, RNA virus of the Picomaviridae family, is predominantly spread by the faecal-oral route and is not associated with risk factors that suggest frequent blood-borne transmission. Following inoculation, virusemia is present and for an average of 3 weeks before the onset of biochemical or clinical hepatitis. Several reports of transfusion-associated hepatitis A have appeared. Outbreaks of HAV have occurred in haemophiliacs, after the use of pooled factor VIII prepared with solvent-detergent methods, as this treatment is not effective against non-enveloped viruses such as hepatitis A. In South Africa, a single batch of imported plasma used for the manufacture of factor VIII concentrate, using the solvent-detergent method, was contaminated with the virus. Although the starting pool contained neutralising antibodies, these were removed by the purification process, suggesting that the contaminated virus may have escaped neutralisation. The blood products advisory committee of the US Federal Drug Administration (FDA) have, however, concluded that the possibility of HAV transmission by blood products prepared with solvent-detergent methods using good manufacturing practice is remote.25 Haemophiliacs should be protected from this possibility by vaccination. In South Africa, close to 100% of subjects from poor socio-economic circumstances have antibodies to HAV by age 6. In contrast, only one-third of subjects from higher socio-economic backgrounds have antibodies by age 20. Individuals from this group are at risk for transfusion-associated hepatitis A.

### Recommendations

There are no effective methods to screen donors for HAV. Product manufacture, by any accepted method, including solvent detergent preparation, should follow guidelines for good manufacturing practice. Non-immune haemophiliacs should be vaccinated against HAV and the epidemiology of HAV infection in this group should be documented.

### Management of donors testing positive for a hepatitis virus

#### Hepatitis B

Acute hepatitis B infection is suggested by recent onset of symptoms, a marked increase in serum transaminases, and the absence of clinical features of chronic liver disease. HBsAg is present in more than 80% of acute infections, but may be cleared during the symptomatic phase, especially in acute severe disease, or in minor infections. IgM anti-HBc identifies the majority of HBV infections in the window phase where HBsAg is negative. Occasionally, no serum markers are detectable. Single tests for HBSAg and anti-HBc have no value in discriminating between acute and chronic hepatitis B.

Chronic HBV is diagnosed if HBsAg remains present for more than 6 months and is suggested by HBsAg persisting for more than 12 weeks. Aminotransferases are raised in most cases of ‘active’ HBV infection, while the ‘inactive’ carrier state is characterised by normal aminotransferases, absent HBsAg and absent HBV-DNA. Viral replication, the marker of active disease, is shown by the presence of HBsAg and HBV-DNA in the serum. Pre-core mutants may not express HBsAg, but raised transaminases and HBV-DNA are present in serum.

In chronic disease, liver biopsy should be done to assess the stage and activity of the disease and confirm the diagnosis of HBV. However, treatment recommendations can be made when biopsy is contraindicated. The hepatic inflammatory activity and degree of fibrosis should be scored and the terms ‘chronic active’ and ‘chronic persistent’ hepatitis should be avoided.

#### Treatment

**Alpha-interferon (INF-α).** INF-α has been shown in randomised controlled trials to be effective in inducing remission in 25 - 40% of patients with chronic hepatitis B. The largest trial, a collaborative study of 169 patients in the USA, showed that 5 million units (MU) INF-α subcutaneously daily for 4 months induced sustained remission in 37% of patients vs. 7% of controls, while 1 MU daily induced remission in only 17% of patients. A 25 - 40% remission rate was found with the use of 5 MU/m² or 9 - 10 MU 3 times a week for 3 - 6 months. Both recombinant and lymphoblastoid IFN-α are effective. The optimal dose of INF-α therapy is still uncertain. However, successful therapy generally requires a minimum of 3 months of treatment. Side-effects are usually tolerable at doses of 5 MU daily in clinically compensated patients. Treatment 3 times weekly inhibits viral replication as effectively and is better tolerated than daily dosing, while relatively low doses (5 - 10 MU/m²)
are as effective as and better tolerated than high doses (36 - 48 MU daily).

The pretreatment serum HBV-DNA concentration is the most important predictor of response to IFN-α in patients who are HBeAg-positive. Patients with low levels (< 100 pg/ml) respond much more readily than those with high levels (> 200 pg/ml). An appropriate regimen to begin with would be 5 MU/m² of INF-α 3 times a week for 4 months in patients with low levels of HBV-DNA and higher doses (10 MU/m²) in patients with high HBV-DNA levels.

Long-term follow-up has shown that remission (loss of HBeAg and HBV-DNA) is usually sustained. A good response to INF-α in patients with hepatitis B is said to have occurred when there is a sustained loss of HBeAg and of HBV-DNA from serum, together with a sustained normalisation of aminotransferase activity. Complete remission is associated with loss of HBeAg.

HBV-DNA usually falls sharply 2 - 3 months after initiation of therapy, but may remain detectable for several months during the course of IFN-α. In contrast, HBeAg may only be lost up to 12 months after completion of therapy. As quantitative HBV-DNA measurements (using standardised techniques, e.g. molecular hybridisation) become more readily available, HBV-DNA should replace HBeAg measurements. Ten to fifteen per cent of subjects who clear the virus during therapy may relapse. This is more common in immunosuppressed subjects and those with variant viruses or unusual serology and advanced disease.

Retrospective analyses have shown that certain subjects are more likely than others to respond to INF-α. These include patients with serum aminotransferase activities more than twice the upper limit of normal, low circulating levels of HBV-DNA, absence of immune suppression, HIV, renal failure or immunosuppressive therapy, a short duration of HBV infection, or a history of acute symptomatic hepatitis; non-Asians; and females. However, subjects should not be precluded from therapy because the probability of a remission is reduced, as significant numbers of patients respond despite the presence of unfavourable features. The cost, potential risks and benefits of therapy, and the risks of non-treatment, should be fully discussed and an informed decision made by the patient in consultation with the doctor.

Corticosteroid pretreatment was used in some studies in an attempt to increase responsiveness to INF-α, but these failed to show consistent improvement in response rates over interferon alone. Corticosteroids may exacerbate chronic HB disease, and exacerbations may be life-threatening. They are therefore no longer recommended.

Therapy in cirrhosis is associated with increased side-effects, the flare of activity caused by therapy may be severe and life-threatening, and sustained response is unlikely in advanced Child's C disease. Despite this, beneficial responses have been noted in up to 35% of cases. Since there are currently no therapeutic alternatives, and transplantation is excluded in patients with actively replicating virus, therapy should be considered. Treatment should be reserved for early or mildly decompensated cirrhosis and should only be given by physicians experienced in the use of interferon. To start, doses of no more than 1 MU 3 times a week should be used. Doses may be increased depending on tolerance. Careful monitoring for bacteraemia, cytopenias, psychiatric side-effects and decompensation of cirrhosis must be undertaken.

Children less than 16 years of age frequently have mild disease with low aminotransferase levels and a poor response to interferon. However, they tolerate interferon well, and those with moderate to severe disease respond as well as do adults. Children who have aminotransferases more than 1.5 times the upper limit of normal, positive HBeAg and HBV-DNA should therefore receive 5 - 10 MU/m² 3 times a week for 16 - 24 weeks.

Patients with normal or minimally raised aminotransferases rarely have significant underlying liver disease and little benefit can be expected from therapy. In addition, response rates to interferon are poor. These patients should therefore generally not be treated. However, those with extrahepatic manifestations, e.g. glomerulonephritis, have greater benefit and higher response rates and warrant therapy.

Patients with active hepatitis as a result of pre-core mutants have raised transaminases, HBSAg and HBV-DNA in their serum but lack HBeAg. Any patient with raised transaminases and HBSAg in the serum, but negative HBeAg, should therefore have HBV-DNA levels measured. While the prevalence of HBeAg-negative pre-core mutants in South Africa is unknown, HBV-DNA has been detected in approximately 6% of HBSAg-positive, HBeAg-negative HBV infections at Ga-Rankuwa hospital, indicating that such variants are probably present in South Africa. Although response rates to INF-α therapy may be slightly lower and relapse rates after completion of therapy greater than in HBeAg-positive cases, several controlled trials have shown therapy to be beneficial. Response is determined by normalisation of aminotransferases, disappearance of HBV-DNA and loss of HBCAg from hepatocytes, as shown by immunohistochemistry.

Where an adequate initial course of therapy has been given, retreatment is of little value in interferon non-responders.

The major early side-effects of interferon may include an influenza-like syndrome, chills, fever, malaise, muscle aches and rigors. Later side-effects may include malaise, muscle aches, headaches, poor appetite, weight loss, increased need for sleep, psychological effects (irritability, anxiety, depression) hair loss, thrombocytopenia and leucopenia. Unusual or severe side-effects include seizures, acute psychosis, bacterial infections, auto-immune reactions, thyroid disease, proteinuria, myocardiopathy, skin rashes and interferon antibodies. Patients should be monitored at 1 - 4-weekly intervals during treatment and blood counts and serum aminotransferase activity should be measured at these intervals. Thyroid function should be measured before, during and at the end of therapy.

Dose reductions are required where side-effects are intolerable but not life-threatening (severe fatigue, irritability, bone marrow depression). Doses are reduced by 25 - 30%. Early discontinuation of therapy, for marked depression or anxiety, psychosis, seizures, hepatotoxicity (or exacerbation of disease) or because of severe bacterial infections, may be required in 5 - 10% of cases.

The primary reason for monitoring hepatitis B status during interferon therapy is to establish which subjects are unlikely to respond and therefore where therapy can be stopped early to save cost and reduce the risks of ongoing treatment. HBV-DNA levels should be measured at 2
months, using a standardised quantitative assay, and if they have not dropped by more than 25%, the patient is unlikely to respond and interferon can be stopped. In general, measurement of liver function tests and of HBsAg and HBsAb provide little useful information during therapy and are costly: they should not be done unless specifically indicated. Viral markers and liver function tests should be obtained at the beginning and end of therapy and 6 - 12 months after completion of therapy, to assess whether a sustained response has occurred.

Other forms of therapy. A large variety of immunomodulatory and antiviral therapies have been used in an attempt to improve on the 30 - 40% response rate of INF-α. The immunomodulatory agents showed promising effects but failed to induce long-term remissions, and response rates of the combination of these agents and interferon have to date been lower than those with interferon alone.

Hepatitis C

All subjects with hepatitis C antibodies should be referred to a physician who is knowledgeable about the virus and the interpretation of its serological studies and has access to appropriate laboratory investigations. The diagnosis of HCV infection should be confirmed, complications sought, and counselling, management and follow-up instituted.

Diagnosis

Because less than 20% of blood donors with positive HCV-antibody screening tests have evidence of true infection, the clinical significance of positive antibodies on EIA should be established using recombinant immunoblot assay (RIBA) or polymerase chain reaction (PCR) to confirm viraemia, and inflammatory activity estimated using aminotransferase levels. Subjects with positive RIBA or PCR, or those with abnormal aminotransferases, should have a liver biopsy to establish inflammatory activity and the degree of fibrosis.

Therapy

HCV causes low-grade but insidiously progressive disease, which seldom remits spontaneously. Up to 40% of patients may develop cirrhosis or hepatocellular carcinoma. Therapy is aimed at arresting activity and clearing the virus, to reduce symptoms and prevent these long-term complications.

INF-α. INF-α is recommended for patients with serological markers for hepatitis C, persistently raised aminotransferases and chronic inflammatory activity on histology (portal inflammation, piecemeal or bridging necrosis) but without cirrhosis. Patients with HCV cirrhosis tolerate INF-α poorly and seldom have a response. The long lead-time before complications occur, due to the low-grade course of the disease, suggests that the threshold for treating younger people (< 40 years) should be lower than that for older patients.

Numerous trials have shown that INF-α 3 - 5 MU 3 times a week subcutaneously for 16 - 24 weeks normalises aminotransferases, clears HCV-RNA from serum and improves histology in approximately 50% of patients, but half of these relapse within 6 - 12 months of completion of therapy with reappearance of HCV-RNA and raised aminotransferases (20 - 25% overall complete response). Higher doses (5 - 6 MU, 3 times a week for 9 months, followed by 3 MU, 3 times a week for 9 months, or 5 MU, 3 times a week for 48 - 52 weeks) have been associated with complete response rates of up to 50%.

A partial response to interferon has been defined as the normalisation of aminotransferases, disappearance of HCV-RNA and disappearance of histological signs of inflammatory activity on treatment, but recurrence of HCV-RNA and biochemical and histological markers of inflammatory activity within 12 months after completion of therapy. A complete response is characterised by sustained loss of HCV-RNA, sustained normalisation of aminotransferases and sustained histological normalisation, more than 12 months after completion of therapy.

Statistically, patients without cirrhosis who have a short known duration of abnormal aminotransferase activity, type 2a genotype (Simmonds) (type 1b have poor response), low HCV-RNA levels and low numbers of circulating quasispecies do best. However, no predictors of response are helpful for individual patients. Patients who meet the criteria for treatment should receive therapy and the response should be monitored, irrespective of the presence of predictive markers.

Safety monitoring should be the same as for interferon use in hepatitis B (see above). Patients with auto-immune disease associated with HCV may have exacerbation of disease, and should be monitored for increases in transaminases.

Patients with HCV have an increased prevalence of auto-immune markers, while false-positive HCV may be found in auto-immune hepatitis. Some patients with PCR-confirmed HCV infection and positive auto-immune markers, may lose their HCV-RNA and display features typical of auto-immune hepatitis. Patients with HCV antibodies and auto-immune markers should have the diagnosis of HCV confirmed by RIBA or PCR. If the confirmatory tests for HCV are negative, these patients should be treated as for auto-immune hepatitis with corticosteroids. Even if HCV confirmatory tests are positive, many patients may have exacerbations of disease on interferon. INF-α should be stopped and they may benefit from corticosteroids.

Patients with normal aminotransferases probably have benign disease with low-grade hepatitis, and should only be treated if hepatitis becomes more active as shown by raised transaminases or histology.

Children have similar response rates to adults. The threshold for treatment should probably be lower in children, as the virus is seldom cleared spontaneously, and they have potentially greater lead-in time for developing cirrhosis and hepatocellular carcinoma.

Patients with cirrhosis respond relatively poorly to interferon. Side-effects are more common and serious and include bacterial infections and psychological problems.

Only well-compensated cirrhotics should be considered for therapy.

Oncology patients and patients with solid-organ transplants or HIV or on renal dialysis are at increased risk of carrying HCV and frequently have higher viral loads and
more active disease. No controlled data are available and therapy is not indicated outside of controlled clinical trials. There are currently no guidelines for re-treating patients who have either relapsed or have not responded to an initial course of therapy. Patients who have relapsed may benefit from long-term therapy with higher initial doses (e.g. 5 - 6 MU 3 times a week for 3 months, followed by 3 MU 3 times a week for 9 months), or from long-term low-dose suppressive doses of INF-α (1 MU 3 times a week). There is no evidence that patients benefit from a second course of therapy if they have not responded to the first. These therapies should only be given within a controlled trial setting.

Ribavirin. A multi-centre controlled trial of ribavirin has shown that while transaminases improve during therapy, there is no effect on viral load or HCV clearance. The combination of ribavirin and interferon is currently being investigated.

Conclusion
TAH has been remarkably reduced as a result of careful donor selection, screening for hepatitis B and C and viral inactivation procedures employed in pooled product preparation. Constant vigilance and attention to detail are required for continued safe blood product provision. A prospective surveillance study for TAH is essential to determine the prevalence of hepatitis B that may be missed by basic HBsAg screening and of HBNC hepatitis. Further studies are required to determine the most accurate methods of HCV screening. Patients with TAH or donor testing positive for these viruses should be referred to physicians with specialised knowledge of hepatitis who can, where appropriate, institute treatment with interferon.

REFERENCES
Is the use of recombinant human erythropoietin in anaemia of prematurity cost-effective?

M. P. Meyer, C. Haworth, L. McNeill

In a double-blind placebo-controlled study we showed a 3-fold decrease in blood transfusions (BTFs) given to preterm infants with anaemia of prematurity who received recombinant erythropoietin. However, only 50% of placebo recipients required a BTF. Data from the placebo group indicated that either mean daily weight gain < 7.5 g/day before study entry or haematocrit < 50% at birth was associated with BTFs (P < 0.001). We calculated that giving recombinant erythropoietin to patients in the treatment group with either of these variables prevented 24 of 28 BTFs and that it would cost R184 to prevent 1 BTF. The cost of each BTF was R187 (blood filtered to remove white cells and reduce cytomegalovirus transmission). Therefore, the costs of the two treatments were similar, but as the risk of transmission infection is lower with erythropoietin, we recommend its use in selected preterm infants.


Recombinant human erythropoietin (rHuEpo) decreases blood transfusion (BTF) requirements in preterm infants with anaemia of prematurity. The European multicentre study showed a 1.4-fold reduction while a double-blind placebo-controlled study carried out at Groote Schuur Hospital demonstrated a 3-fold decrease in transfusions in the treatment group.

In the latter study, however, only 19 of 39 (49%) infants in the placebo group received one or more BTFs during the study period. Other workers have reported similar findings. Therefore, the treatment of all preterm infants < 33 weeks’ gestation with rHuEpo results in unnecessary use of the drug and increases the cost significantly.

We sought retrospectively to identify a group of preterm infants at higher risk for BTF and to compare the costs of rHuEpo and BTF in such infants. We asked the following questions: (i) were there risk factors for BTF among the preterm infants in the placebo group (identifiable prior to study entry?); (ii) would the use of rHuEpo reduce BTFs in patients with these risk factors?

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