Therapeutic venesection at the Australian Red Cross Blood Service: impact of the High Ferritin Application on management of hereditary haemochromatosis

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Background

Therapeutic venesection is an established treatment for hereditary haemochromatosis. The C282Y homozygotes and C282Y/H63D compound heterozygotes are the most likely human haemochromatosis protein (HFE) variants to cause iron overload. The principal indications for treatment include iron overload, which is detected through measurement of hepatic iron concentration or a liver biopsy, or suspected iron-overload on the basis of elevated serum ferritin levels. Venesection is not indicated for other HFE genetic variants or in patients with isolated hyperferritinaemia in the absence of the main HFE gene mutations. The Australian Red Cross Blood Service provides a therapeutic venesection program. Since January 2013, referral has been conducted electronically using the novel, web-based High Ferritin Application.

Objectives

The aim of this article is to provide information regarding implementation of the High Ferritin Application and document its impact on referral patterns.

Discussion

This referral process is based on nationally endorsed, evidence-based algorithms, which have markedly reduced the number of unnecessary therapeutic venesections. An estimated 4000 unnecessary venesections are averted each year and this equates to a saving of $1.4 million.

Therapeutic venesection is a treatment modality for hereditary haemochromatosis, polycythaemia vera and porphyria cutanea tarda. Hereditary haemochromatosis is the most common cause of iron overload in Australia and primarily occurs in populations of Northern European descent (prevalence 1:190).[1] This is the result of a C282Y homozygous mutation in the HFE gene product.[1] Up to 40% of men and 13% of women with this genetic disorder may develop clinically significant iron overload.[2] The more common C282Y/H63D compound heterozygous genotype is now known not to increase the risk of significant iron overload.[3,4]

Hereditary haemochromatosis is a relatively common indication for venesection treatment. The Australian Red Cross Blood Service performed 37,750 therapeutic venesections in the 2013–14 financial year alone, according to the internal blood service reporting.

The Australian Red Cross Blood Service has a long-established therapeutic program, which provides a venesection service for patients whose blood may often be used in blood products. The patient's blood is discarded if it is not suitable for clinical use. In 2013–14, 7325 donations (19% of therapeutic venesections) were discarded.

The Australian Red Cross Blood Service introduced the web-based High Ferritin Application (the App; https://highferritin.transfusion.com.au) in January 2013. This application allows doctors to refer patients to the Australian Red Cross Blood Service for therapeutic donation, receive real-time responses and access current educational material. Patients receive an appointment schedule within 48 hours of the referral.

Background to development of the App

The Australian Red Cross Blood Service is funded by the Australian Federal Government, through the National Blood Authority (NBA), to provide a therapeutic venesection service when it is medically appropriate. Prior to January 2013, referrals from specialists and general practitioners (GPs) for this service were paper-based. The paper-based system was found to be resource-intensive and inefficient, and referrals were often non-evidence-based.

An electronic tool that provides a real-time response was developed in collaboration with Professor John Olynyk, an expert in disorders of iron metabolism. The algorithms that underpin the criteria for acceptance into the Australian Red Cross Blood Service therapeutic program were based on current evidence.[5,6] The algorithms were endorsed by the Gastroenterology Society of Australia, the Haematology Society of Australia, and New Zealand and Haemochromatosis Australia.

Functionality

When a referral using the application meets the Australian Red Cross Blood Service's therapeutic acceptance criteria, the referring clinician is notified in real-time. A file with the patient's details and venesection schedule is then sent to a secure server that can only be accessed by the Australian Red Cross Blood Service contact centre. Staff at the contact centre then arrange the venesection schedule for the patient.

Patients who do not meet the application's criteria may be referred as volunteer blood donors, or may need further investigation through routine clinical services in the community.

Educational material regarding high ferritin and iron overload are also available through the application. The other option would be to request individual assessment for patients with unusual causes of verified iron overload. Patients with polycythaemia vera or porphyria cutanea tarda who require therapeutic venesection may also be referred through the application.

The application is supported by a help desk. Referring doctors can obtain assistance through email or telephone if they have any difficulties in using the application. The help desk provides administrative, technical and medical assistance. The help desk can also access specialist opinion for requests for individual assessment of iron overload states that do not meet the criteria.

Communications strategy for referring clinicians prior to launch of the App

The 3865 doctors who referred to the therapeutic program 2 years before the App was live were informed of the new referral method by letter.

Paper-based referrals received when the application went live were processed, but a letter was sent to the referring doctor advising of the new process. Referrals received after 30 April 2013 were returned with a letter explaining the new process.

An article about iron overload and high ferritin, which noted the new algorithm and referral process, was published in late 2012.[5] The Australian Red Cross Blood Service presented updates at the 2012 General Practitioner Conference and Exhibition in Sydney, and provided an online education session that attracted 7037 views.[7]

Data collection and analysis

Data were collected from the Australian Red Cross Blood Service tracking documents between May–July 2012 to examine paper-based referral patterns prior to the application going live. Therapeutic data from May–July 2013 were collected from the application to obtain web-based referral data.

The number of new referrals received between May–July 2012 was 1155, of which 189 (16.4%) did not meet the criteria and therefore were not admitted to the program (*Table 1*). The number not accepted through the paper-based referral system were represented in all categories, although the majority were in the 'data not captured' or 'non-iron-overload genotypes' groups. An additional 334 patients, who would not have been admitted to the program if the App had been in place, were venesected. This figure may underestimate the true number of inappropriate admissions to the program prior to the application as 442 (38.8%) referrals have incomplete data recorded.

The number of referrals received during the study period in 2013 was 901. Non-compliant referrals cannot be quantified, but are likely to represent a significant number of patients who no longer undergo unnecessary venesection. In addition, this paperwork does not require processing by the Australian Red Cross Blood Service. It is important to note that there was a marked increase in the number of patients who were eligible for treatment, being either homozygous or compound heterozygous for causative HFE mutations.

Referral using the application has resulted in only patients with evidence-based indicators being admitted to the therapeutic program. While venesection is a very safe procedure, it exposes

Table 1. Referral patterns comparing May–July 2012 paper-based and May–July 2013 electronic referrals

Year	Referrals	C282Y homozygote	C282Y/H63D compound heterozygote	Genotypes not associated with iron overload	Data not captured
2012	1155	217 (18.8%)	162 (14.0%)	334 (28.9%)	442 (38.3%)
2013	901	630 (69.9%)	270 (30.0%)	0 (0.0%)	1 (0.1%)

patients to risk and should therefore not be performed unless necessary. Whole-blood donation may be complicated by vasovagal reactions (found in 2.5% of donations) or phlebotomy injury (found in 0.2% donations), but the vast majority of these events are minor and self-limiting. However, donors may suffer secondary injuries as a result of falling due to a vasovagal reaction and may occasionally suffer a nerve injury due to phlebotomy trauma. Unnecessary exposure to these complications has been averted by restricting therapeutic venesection to patients whose condition meets current evidence-based criteria.

A minimum of 334 (28.9%) therapeutic donors who would not meet current criteria were accepted for venesection during the study period in 2012. The average annual number of donations per therapeutic donor is 3.04 and 19.4% of donations are discarded. The notional cost for a whole-blood collection is $347 (based on the NBA's price per unit of red blood cells). Approximately 4000 unnecessary venesections are averted each year and this equates to $1.4 million in avoided cost. An estimated cost of $300,000 is averted if no products can be used and the blood is discarded.

The mean age of patients referred during 2012 and 2013 was statistically different (P <0.05), with the mean age in the App referral set 3.1 years lower than the paper-based set. This finding is consistent with the change in referral pattern to patients with true iron-overload-related genotypes as opposed to older patients with raised ferritin who have non-significant HFE variants.

There was a higher percentage of males in the application referral group, which is also consistent with a cohort of more appropriate referrals (*Table 2*).

Table 3 shows the marked reduction in the time from referral to appointment and a decrease in rates of failure to attend. This improvement is due to the successful electronic referrals being actioned directly by the Australian Red Cross Blood Service contact centre and not requiring time-consuming assessments by medical officers.

Implementation issues

Feedback was received from referring doctors. During the 12-month period ending in August 2014, 4308 referrals were received from 2338 registered doctors. The total number of doctors registered on the App on 17 September 2014 was 4172.

Table 2. Patients' characteristics comparing May–July 2012 paper-based and May–July 2013 electronic referrals

Year	Mean age (years)	SD	Males (%)	Ferritin (µg/L)
2012	50.1	14	62.6%	547*
2013	47	13	66%	200–499†

**Paper-based referral data provided a discrete ferritin level: this figure represents the mean ferritin level for referrals during the 2012 period.*
†Data collected through the App provided a range; the greatest frequency of referrals (35%) occurred in the range 200–499 µg/L

Table 3. Referral outcomes comparing May–July 2012 paper-based and May–July 2013 electronic referrals

Year	Mean referral appointment (days)	Percentage who did not attend
2012	91.3	37.5%
2013	19	17%

Refinements were made when recurrent or significant issues related to operation of the App were identified.

Concerns regarding the compliance of the application with privacy legislation and information security have been addressed by incorporating stringent security measures. These measures are based on expert legal and information systems advice:

- The App resides on a secure server within Australia and is protected by a firewall.
- Information contained in the application is encrypted and information of individual patients is only accessible to clinicians who manage those patients.
- The App itself does not message the patients or the Australian Red Cross Blood Service with patient-related information. Data related to patients for the purpose of booking venesection appointments are downloaded weekly. Access to these data is protected by a username and password specifically for the use of the in-house contact centre.
- Daily encrypted back-up of data is undertaken and stored off-site.

Conclusion

The High Ferritin Application has proven to be very successful since becoming operational in January 2013. There have been significant cost savings and efficiency gains from the Australian Red Cross Blood Service perspective. Accepted referrals now comply with current evidence-based practice:

- hereditary haemochromatosis: C282Y homozygotes, C282Y/H63D compound heterozygotes
- other hereditary haemochromatosis genotypes only where iron overload is established (eg by MRI measurement of hepatic iron concentration)
- polycythaemia vera
- porphyria cutanea tarda.

The donor is contacted within 48 hours of referral (a 97% improvement) and generally attends an appointment within 19 days. There is now no regional variation in terms of referral quality and processing.

The App will continue to be refined based on feedback and performance. Cost savings will be ongoing as the only recurrent costs are for the help desk (already part of the medical services budget), and costs associated with server hosting and updating the App.

We believe the App may provide a model for other process and efficiency improvements within the Australian Red Cross Blood Service, and in the general medical and hospital community, especially where evidence-based clinical pathways exist.

Australian governments fully fund the Australian Red Cross Blood Service for the provision of blood products and services to the Australian community.

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References

1. Olynyk JK, Cullen DJ, Aquilia S, Rossi E, Summerville L, Powell LW. A population-based study of the clinical expression of the hemochromatosis gene. New Engl J Med 1999;341:718–24.
2. Allen KJ, Gurrin LC, Constantine CC, et al. Iron-overload-related disease in HFE hereditary haemochromatosis. New Engl J Med 2008;358:221–30.
3. Bacon BR, Olynyk JK, Brunt EM, Britton RS, Wolff RK. HFE genotypes in patients with hemochromatosis and in other liver diseases. Ann Intern Med 1999;130:953–62.
4. Gurrin LC, Bertalli NA, Dalton GW, et al. HFE-compound heterozygotes are at low risk of hemochromatosis-related morbidity. Hepatology 2009;50:94–101.
5. Goot K, Hazeldine S, Bentley P, Olynyk J, Crawford D. Elevated serum ferritin – What should a GP know? Aust Fam Physician 2012;41:945–49.
6. Ayres LRO, Jayasekeran V, Olynyk JK. Genotype–phenotype relationship in hereditary hemochromatosis. In: eLS. Chichester: John Wiley & Sons, Ltd, 2013.
7. Olynyk JK. Managing patients with high ferritin – Education discussion: ThinkGP. Available at http://thinkgp.com.au/education/content/20877 [Accessed 31 March 2013].

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