Development and exploitation of a clinical decision support system for the management of renal anaemia

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Abstract
The management of renal disease and its comorbidities lends itself to the use of computer-assisted decision support systems (CDSS); however, several issues with regard to computer-based treatment algorithms remain unresolved. This review examines the development and application of a clinical decision support system for the management of renal anaemia. Studies illustrate the dependence of outcome on prespecified haemoglobin (Hb) intervention values (thresholds) and the use of a computer program containing treatment algorithms to manage Epoetin doses and iron supplements. Early experimental studies and randomized, controlled studies are discussed that examine the use of clinical measures of haemodialysis (HD) and peritoneal dialysis (PD), including Hb, serum ferritin and red cell hypochromia or transferrin saturation. Broad flexibility of erythropoietic agent, dosing, route of administration and frequency has been built into computer programs written for clinical and experimental application. While further studies with the system are anticipated, predictability and sustainability of Hb outcomes and a capacity to manage large patient groups have been demonstrated and wider application appears promising.

Keywords: anaemia management; erythropoietin; haemodialysis; haemoglobin; iron deficiency; peritoneal dialysis

Introduction
In the management of renal anaemia, both the cost of erythropoiesis-stimulating proteins (ESPs) and the clinical effort needed to manage large numbers of renal patients have been important drivers in the search for a systematic solution to control haemoglobin (Hb) levels. In the mid-1990s, there was an increasing awareness in the United Kingdom (UK) renal care community of suboptimal outcomes in the management of renal anaemia. The development of systematic literature reviews and guidelines resulted in the publication of treatment ‘standards’ for clinical outcomes by the UK Renal Association (UKRA) [1]. These standards took the broad range of outcome variables into account and recommended the achievement of Hb values in a certain fraction of the patient population after a treatment interval. For example, the goal for anaemia management was Hb levels above 10 g/dl in 85% of the HD patient population (Figure 1).

In a pilot study, the UK Renal Registry (UKRR) published Hb point prevalent data from several renal units that were expressed quantitatively by summary statistics [2]. Examination of the Hb results for individual centres in the UKRR data revealed a Gaussian (normal) distribution to be typical, with unexpectedly uniform standard deviations (SDs) of around 1.5 g/dl. Based on these results, it was apparent that a group mean Hb of 11.5 g/dl would be required to account for such variability (i.e. SD), so that Hb levels were >10 g/dl in 85% of the HD patient population [3] (Figure 2). This was subsequently confirmed by others [4].

With a growing chronic kidney disease (CKD) population in many countries, it was of real interest to reduce the logistical effort of anaemia management for this group of patients, if possible. However, it was unclear how to achieve a particular Hb population distribution deliberately and predictably, especially using a ‘targeting’ model of clinical management. While practical advice was available for the management of individual patients, there was no information in the literature on how a renal centre might achieve prespecified Hb goals using validated techniques. It was not useful to literally aim for the average value since there was no reason to believe that the outcomes would fit those required by the UKRA Standards, for example [5]. Furthermore, studies indicated that the use of deliberate targets in clinical
Fig. 1. Data from the United Kingdom Renal Registry 1999: percentage of haemodialysis patients achieving the Renal Association treatment standard (compliance with 85% >10 g/dl for haemoglobin). Renal units (N = 18) are identified by alphabetical characters in this early example of comparative audit, with the missing data points given below the letters. Summary statistics are given by mean and confidence intervals, with the standard error shown as a missing data point below the letters. Summary statistics are calculated as mean and confidence intervals, with the standard error shown as a missing data point below the letters.

Fig. 2. Idealized Gaussian curve showing the calculated mean required to achieve 85% of values greater than a chosen minimum (normal distribution mean—1SD) [20].

Developing algorithms for epoetin therapy and iron supplementation

Protocols for epoetin therapy

We designed two randomized, controlled studies to investigate the consequences of setting lower threshold and ceiling Hb values for a change in epoetin-β therapy, i.e. lower and upper Hb limits that would prompt an increase or decrease, respectively, in ESP dosage [8]. These thresholds were based on the known desirable Hb mean of 11.5 g/dl. In the first study, unselected HD patients (N = 236) were randomized to monthly intervention if their Hb levels fell below 10.5 g/dl (Group A) or 11.5 g/dl (Group B). The ceiling Hb limit was set at 14.0 g/dl for both groups. The epoetin-β dose adjustments were implemented based on a ‘ladder’ regimen using increments and decrements of 3000 IU/week, given in three divided doses. A 50% reduction in dose was used to lower Hb levels above 15.5 g/dl. All intervention values were within conventional treatment ranges and within the safety parameters of clinical management. After 6 months of the study, the mean Hb was 11.1 g/dl in Group A and 11.7 g/dl in Group B (P = 0.001), with no significant difference between the two groups in SD (1.7 g/dl vs 2.1 g/dl, respectively) (Figure 3). Also, there was no difference between the two groups in the mean epoetin dose.

After an 8-month washout period with a unified lower threshold of 11.0 g/dl, unselected haemodialysis patients (N = 211) were entered into a second study, rerandomized and assigned to groups according to an Hb ceiling of 12.0 g/dl (Group C) or 13.0 g/dl (Group D) [8]. Dose adjustments were based on the same ladder regimen. At 8 months into the second study, mean Hb levels were 11.5 g/dl and 12.2 g/dl for patients in Groups C and D, respectively (P = 0.03). There was a significant difference between the groups in SD (1.37 vs 2.07, respectively, P < 0.001), but the mean epoetin dose remained the same. In this context, Hb variability as measured by group SD was effectively reduced.

These studies allowed the prediction that lower and upper Hb intervention thresholds of 11.0 and 12.0 g/dl, respectively, would give a mean population outcome of 11.5 g/dl with 85% of patients above 10.0 g/dl.

Protocols for iron supplementation

Iron is essential for the formation and function of Hb. Supplemental iron therapy can be a cost-effective practice did not always improve renal disease management, haemodialysis Kt/V being the most characterized [6]. On the other hand, there were some examples in the literature in which the use of range limits as thresholds for dosage change seemed to improve results [7].

At Leeds, St James’s, the haemodialysis patient group was generally iron-depleted and tended to demonstrate declining Hb values. Their management overall was highly uniform, including the administration of subcutaneous (SC) epoetin-β at the time of protocol-based haemodialysis. In the clinic, as everywhere, Hb control was being attempted by clinician-initiated changes of ESP dosage at various Hb values (notional thresholds), according to the perceived Hb trend and ESP responsiveness. We proposed that by fixing the threshold values at which dose changes were made for an entire patient cohort and standardizing the ESP dose ‘ladder’, we might be able to fix the desired group outcome distribution without necessary detriment to individuals [8]. The problem remained to find just what threshold values might produce a particular outcome. Subsequently, we developed a computer-based decision support system (CDSS) for anaemia management that recommended doses for ESP and supplemental iron therapies to achieve Hb control. Dose recommendations were based on treatment algorithms that utilized threshold and ceiling prompts. In the remaining part of this review, we discuss our experience with the development and implementation of this system at our centre.
method of improving Hb levels [9]. Unfortunately, iron deficiency is common in the HD population. The current European Best Practice Guidelines (EBPGs) recommend serum ferritin levels $>100$ ng/ml and hypochromic red cells (HRC) $<10\%$ in order for patients to maintain adequate Hb control [10].

In an earlier prospective study, we had investigated the effectiveness of IV iron therapy in a group of HD patients ($N=82$) with anaemia and iron deficiency [11]. In this population, Hb levels were $<10$ g/dl and serum ferritin was $<100$ $\mu$g/l, despite oral iron therapy. The epoetin dose was not adjusted. Patients were administered supplemental iron therapy with IV iron saccharate (200 mg/week) over 8 weeks. Significant increases from baseline were observed for both Hb (8.9 ± 1.0 to 10.1 ± 1.4 g/dl, $P < 0.0001$) and serum ferritin (55 ± 24 to 288 ± 126 $\mu$g/l, $P < 0.0001$). The magnitude of these increases directly corresponded to the percentage of hypochromic red cells (HRC) prior to treatment so that, in our hands, HRC was a suitable measure for assessing iron status.

**Developing a computer-based decision support system (CDSS)**

Based on the results of our initial studies with epoetin and iron therapy, we developed a CDSS to help clinicians more efficiently manage renal anaemia by maintaining Hb control through optimization of ESP and iron dosing with minimal logistical effort. Input values for this program included Hb level, serum ferritin level, HRC percentage and ESP doses. We conducted a number of prospective studies to assess the effectiveness of this CDSS. The clinical computing system of the unit (PROTON) acquired Hb, HRC and iron data directly from the hospital laboratory computer systems, held prescription records for ESP and iron supplements, and printed actual paper prescriptions for nursing staff action. The recommendations for monthly ESP dose changes were printed in a cumulative format. The entire program could be monitored by a single medical staff member who was aware of the clinical circumstances of the patient group.

**Haemodialysis patients**

We employed the CDSS in a prospective, 24-month study in a cohort of HD patients ($N=228$) with sustained Hb control, per the UKRA recommendations of 85% of the cohort having Hb $>10$ g/dl [12]. We increased the delivered dose of supplemental iron therapy to HD patients stepwise, from intermittent to intermittent plus regular supplements. The treatment algorithm used Hb level, ferritin concentration and HRC percentage to determine the best therapy, and the CDSS provided recommendations for epoetin and IV iron sucrose dosing. To avoid values of serum ferritin over 800 ng/ml (the upper limit from the first EBPG [9]), the CDSS suggested iron supplements be withdrawn if levels exceeded 500 ng/ml. Levels of Hb were maintained with median monthly levels ranging from 11.3 g/dl to 11.8 g/dl. From month 1 to month 24, the median HRC significantly decreased from 8% to 4% ($P < 0.001$) while median ferritin levels increased from 188 ng/ml to a sustained value of 480 ng/ml ($P < 0.001$) (Figure 4). The median epoetin dose decreased from 1361U/kg/week to 721U/kg/week, strongly correlating with the median HRC percentage through the range of $<10\%$. These data indicated that recommendations on controlling Hb levels using a CDSS could be made in a cost-effective manner by adjusting iron and epoetin dosing accordingly, but that additional iron supplementation was less effective in patients who already had adequate HRC levels.

**Peritoneal dialysis patients monthly**

In a second study, we utilized the CDSS to help improve the efficiency of epoetin and iron therapies in PD patients [13]. We treated 103 PD patients in two study periods over 13 months. In the first phase
(months 1–8), patients with iron deficiency [ferritin <100 ng/ml or ferritin 100–500 ng/ml and HRC ≥ 5] were converted from oral to IV iron sucrose at 300 mg monthly. In the second phase (months 9–13), patients with ferritin <150 ng/ml or 150–500 ng/ml and HRC ≥ 2% received IV iron sucrose at 200 mg monthly. In both study periods, treatment regimens were reviewed after 4–8 weeks based on their Hb levels. Subcutaneous (SC) epoetin-β treatment was initiated at 1000 IU thrice weekly if Hb levels dropped below 11.0 g/dl. Dose adjustments were similar to those in our previous studies [12], with intervention initiated at a lower Hb limit of 11.0 g/dl and an upper limit of 13.0 g/dl.

Of the 103 patients, 81 received at least one IV iron infusion during the study. Results demonstrated a non-significant increase in the median Hb from baseline to month 13 (11.0 g/dl–11.7 g/dl). The proportion of patients achieving Hb >11.0 g/dl improved from 51% to 76%, without a significant increase in median epoetin dose (421U/kg/week to 451U/kg/week). The proportion of patients with ferritin <100 ng/ml decreased from 24% to 2% and the median HRC decreased from 4% to 1% (P < 0.01). These findings further supported the principle of pro-active clinical intervention to achieve recommended management goals in a cost-effective manner (Figure 5).

**CDSS application in randomized, controlled clinical trials**

**Dialysis membrane composition study**

The predictability of Hb group outcome delivered by the CDSS was exploited in a randomized controlled trial (RCT) comparing two dialysis membranes to investigate the consequence for Hb control and ESP doses of membrane composition [14]. A unit-wide RCT of HD patients (N = 211) was undertaken, comparing modified cellulose acetate with polysulphone dialysers. An identical delivered Kt/V was established for each group, and the retention of blood in the different dialysers was carefully studied as a possible confounding factor. The results of the 6-month study showed no advantage of the polysulphone for ESP dosing and renal anaemia under these conditions. The Hb outcomes rose in parallel over the study period, proving the capacity of the decision support system to hold the randomized groups to the same Hb values overall. The increase in Hb was probably due to improved dialysis dose under the conditions of the study (i.e. Hawthorne effects plus protocol-delivered dialysis dose changes).

**Dose conversions**

The flexibility of the CDSS system was more recently demonstrated in a 9-month randomized trial comparing weekly SC epoetin-β with weekly SC darbepoetin alfa, after conversion of a group of 217 haemodialysis patients from thrice-weekly epoetin-β [15]. For those patients switched to darbepoetin alfa, we applied a beginning dose conversion factor of 200:1 (epoetin-β: darbepoetin alfa), per the Aranesp European prescribing information (Amgen Europe, Breda, The Netherlands).

The changes in Hb and associated trends were reviewed monthly to ascertain the need for treatment intervention. A clear difference developed between the two groups. At the chosen conversion factor, Hb levels in the darbepoetin group tended to rise and those given epoetin-β showed a fall. These were small changes, but provoked dose recommendations from the system that...
corrected the trends and returned both groups to baseline after the eighth month (Figure 6). As a result, there was a mean dose reduction in the darbepoetin alfa group from 0.59 µg/kg/week at baseline to 0.46 µg/kg/week at month 9 ($P = 0.002$). Conversely, we saw an increase in the epoetin-β dose from 107.5 IU/kg/week to 133.2 IU/kg/week ($P = 0.002$).

**Discussion**

We have demonstrated the effectiveness of Leeds' suite of algorithms in several prospective studies. It is important to note that the studies reviewed here were undertaken in unselected patients (except where consent was not given) at a single centre (Leeds, St James’s), a significant contrast to previously published multi-centre trials. The degree of patient selection in studies may generally be judged by the SD of point prevalent, or mean, group Hb values, greater selection for initial stability being reflected in low values of SD. The general management of anaemia improved through the complete monthly ascertainment of the patient group, with no missed assessments or prescribing. The algorithms have been in continuous use in Leeds for more than 8 years. This has provided economic benefits. The stability of Hb outcomes and ESP usage has allowed predictable, advantageous contracting for the purchase of ESPs at 'facility' level [16], as well as evidence-based decisions on the purchase of dialysis consumables [14].

The PROTON versions have also been implemented at three other large UK renal centres, under a range of ESP conditions, such that both routes of administration (SC and IV), all three available ESPs and several variations of Hb threshold values have been successfully managed [17]. A modification has allowed the replacement of HRC by transferrin saturation (TSAT) in one centre, without difficulty. The achievement of the EBPG guideline for 85% Hb values over 11 g/dl was straightforward, after a planned increase in Hb threshold values [18]. These programmes have now been written in a stand-alone version for more general application (AMIE; Media Innovations, University of Leeds). Flexibility of agent, dosing and frequency are built into the programmes. On the basis of this work, the dosing steps and intervals of sampling of laboratory variables are among the features that need to be further explored experimentally.

A paradoxical effect of this comprehensive system has been that difficult to treat patients (i.e. resistant and/or sick) stand out from the group. The management system acts as a form of clinical sieve, where the lack of routine responses identifies an active clinical issue. The system has also been instrumental in recognizing unexpected clinical issues. For example, one of our four haemodialysis satellite centres (40 patients) was showing unusually high epoetin-β doses recommended by the feedback algorithms, in parallel with declining Hb levels. Careful investigation of blood counts showed no convincing evidence of individual pathology, but concern over water treatment without a carbon filter system led to such filters being installed. There was an early reversal of the Hb and epoetin-β trends, strongly suggesting that chloramine contamination of the water supply had created sub-clinical haemolysis, which had been reflected in turn in the group results in the Hb control system [19].

Potential limitations of this system also should be noted. Recent focus in the literature on the maintenance of desired Hb values, with reduction of individual Hb amplitude and periodicity, is another basis for a range of experimental studies. While the Leeds’ suite of algorithms enables an individual patient to become a component of a predictable population outcome distribution, it has not yet been used to reduce individual Hb variability. Studies have shown that patient populations can achieve Hb levels within a recommended range with the computer-based support system. However, with a minimum Hb value of 11 g/dl, it is inevitable that some very high Hb values will be a consequence because of individual variability, with potential for adverse events and hazard to patients [20]. A series of additional research studies is anticipated to refine the control properties of the system.

**Conclusions**

A computerized management system for the management of renal anaemia was developed from principles based on ESP and iron dose change recommendations at defined threshold values for Hb, serum ferritin and HRC or TSAT. It has been demonstrated to give almost prescriptive unit outcomes in unselected HD populations that can be shaped to satisfy Standards and Guidelines. The methodology ensures patient follow-up. While it may not actually improve already excellent results, it confers the capacity to bring all centres to similar outcomes. That predictability and sustainability is one major benefit, but particularly...
important is the capacity to safely and effectively manage large patient groups in a computer ‘batch’ mode with minimum staff resources. There remain many opportunities for further experimental work with the system.

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Conflict of interest statement. Dr E.J.W. is a Consultant Renal Physician in the Department of Renal Medicine, St James’s University Hospital, Leeds, and undertakes research that is currently supported by Amgen, Inc. Dr C.T. is currently a full-time employee for Amgen Australia Pty Ltd.

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