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An Audit on the Use of Intravenous Iron in the Frail Older Person with Anaemia

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ABSTRACT

Anaemia is common in the older person (greater than 65 years) of which anaemia of inflammation and chronic disease is more prevalent than iron deficiency. Biochemical iron parameters on iron status is compromised in the older person as serum ferritin is increased with age and during inflammation whereas, transferrin saturation can be inappropriately depressed. There are no specific guidelines for intravenous iron for the older person with anaemia. However, the European Society of Cardiology has proposed guidelines in heart failure patients who are iron deficient to receive intravenous therapy. These guidelines also utilised ferritin and transferrin saturation. We elected to explore if these could predict haemoglobin response in the older person.

Method; We examined serum ferritin, transferrin saturation, mean corpuscular volume, C-reactive protein and haemoglobin in anaemic older patients before and 4 weeks post infusion.

Results; Response to iron was observed in subjects with a transferrin saturation of less than 20 and a ferritin to 200 µg/L. For those with a ferritin between 201- 299 µg/L, a haemoglobin response was also observed but attenuated. Mixed anaemia was more common than iron deficiency where improvement was also observed. No response was noted with a ferritin of greater than 400 µg/L.

Conclusions; The European Society of Cardiology guidelines on heart failure with iron deficiency may aid to predict response to iron. Mixed anaemia was common where haemoglobin response was less optimal than in the iron deficiency cohort. Clinicians should resist giving therapy based solely on a low transferrin saturation.

Keywords; Intravenous iron, frailty, iron deficiency, mixed anaemia, ESC guidelines

Glossary of abbreviations

ACD	anaemia inflammation and chronic disease
CAD	coronary heart disease
CKD	chronic renal disease
ESC	European Society of Cardiology guidelines on heart failure with iron deficiency
FCM	ferric carboxymaltose
FDR	ferric derisomaltose
FN	ferritin
Fr	ferroportin
Hb	haemoglobin
IBD	inflammatory bowel disease
ID	iron deficiency
IDA	iron deficiency anaemia
MA	mixed anaemia
IV	intravenous
RE	reticuloendothelial cell
SI	serum iron
STR	serum transferrin receptors
TIBC	total iron binding capacity
TSAT	transferrin saturation
WHO	World health organization
ZPP	zinc protoporphyrin

Introduction

Anaemia is a common entity in the older person (>65 years). It is important due to greater morbidity such as falls, hospitalization, length of stay and mortality.[1] The World Health Organization (WHO) defines anaemia in adults as a haemoglobin (Hb) level <130 g/L in men and <120 g/L in women.[2] However, these values may not be applicable in the older person and there is no widely accepted definition of anaemia for this age group.[3,4]

The two most utilized blood test on iron status is the serum ferritin (FN) and "iron transport apparatus". However, serum FN has a tendency to rise with age even in healthy subjects.[5] The iron transport apparatus: serum iron (SI), total iron binding capacity (TIBC) and TSAT also display deficiencies being labile with hourly diurnal variations and day to day variations.[6,7]

In the older person, anaemia of inflammation and chronic disease (AICD) is far more prevalent than iron deficiency anaemia (IDA).[8] AICD is iron maldistribution (failure of mobilization of body iron stores) where subjects may not be ID and will not respond to iron replacement. Furthermore that the two can co-exists, IDA and AICD or mixed anaemia (MA). Serum ferritin is an acute phase reactant and will be disproportionately elevated in infection/inflammation. During inflammation TSAT is often disproportionally reduced due to the activation of hepcidine which "locks" iron in the recticulo-endothelial cell and within the enterocyte.[5] These further compromise FN and TSAT as assessment tools on iron status.

The European Society of Cardiology guidelines on heart failure and iron deficiency (ESC) stipulates the use of IV iron when (1) serum FN of < 100 µg/L or (2) serum FN of >100-299 µg/L with a TSAT of <20%[10]. Iron therapy can also be given to heart failure patients who are ID but may not be anaemic (fall in Hb occurs much later compared to serum FN or TSAT) and is effective in improving outcomes in subjects with systolic heart failure.

The ECS guidelines preceded validation of iron status using bone marrow studies (regarded as the

gold standard) in subjects with coronary heart disease (CAD) with heart failure. Two recent marrow studies reveal that most subjects (50 percent) were ID but were not anaemic. Serum FN was inferior to TSAT as surrogate markers for ID.[11,12]

There are no guidelines for IV iron with anaemia other than as a second line therapy when oral treatment has failed or in specific disease states such as inflammatory bowel disease (IBD). The aetiology of anaemia in the older person is often multifactorial with a "inflammatory" component. As such, the response of oral iron will be limited due to the activation of hepcidine which impedes iron transfer at the enterocyte bloodstream interface we therefore elected to evaluate the ESC guidelines to determine if it may predict response in ID and MA patients. The gold standard was not undertaken to confirm iron status as we can use the Hb response as a confirmation of ID.

Method

Data on all IV iron supplied to in patients at Ealing Hospital over six months (August 2024 to January 2025) was obtained by running a report on the Pharmacy dispensing system, CareFlow Medicines Management Protocol. This enabled identification of consecutive patients who had received doses of IV iron.

Surgical, orthopedic and gynecological patients were excluded due to blood loss from surgical procedures and blood transfusions. All medical departments were represented except haematology (based on another site of the hospital). There were 210 medical patients of which 85 were analyzed. Exclusions (n=125) were due to (i) those received IV iron and blood transfusions (n=39), (ii) <65 years old (n=37), (iii) No Hb post IV iron (n=16), (iv) given IV iron for heart failure but were not anaemic (n=16), (v) advanced renal disease (serum creatinine >200 µg/L (n=11), and (vi) patients with multiple vitamin deficiencies (vitamin B12 and folate) and iron deficiency (n=6).

We examined serum FN, TSAT, MCV, CRP and Hb, before and at least 4 weeks post IV iron. Anaemia was defined as a Hb of <11g/dl. A response defined as an improvement in the Hb by at least 2g/dl four weeks post IV iron.

Statistical analysis

Results were expressed as mean ± standard deviation (SD). Hb differences within groups pre and at least 4 weeks post therapy were examined using paired student t-test. Differences in Hb between the 6 categories, C1 to C6 were examined using the unpaired student t-test.

Results

Subjects were organized into six categories C to C6. Transferrin saturation were all reduced (<20), Hb < 11g/dl and CRP was raised (>10mg/L). The only variable was FN. Table 1 shows an example of a responder and a non-responder. Steady state was observed (as reflected by serum FN and TSAT) at between 2-3 weeks and improvement in Hb observed at 2 weeks post infusion.

Table 1

Responder							
Age	Sex	Week	Hb g/dl	CRP	MCV mg/L	Ferritin µg/L	TSAT%
91	F	0	102	12	98	33	11
		1	107	10	96	719	36
		2	128	14	97	570	28
		3	127	8	98	250	24
		4	125	12	94	235	24
Non-Responder							
Age	Sex	Week	Hb	CRP	MCV	Ferritin	TSAT
70	F	0	96	316	90	635	6
		1	104	93	90	2585	42
		2	105	23	91	1571	28
		3	110	13	90	1182	30
		4	108	10	91	946	36
		5	106	12	90	916	38
		6	104	14	88	796	32

Top : Responder with weekly Hb, CRP, MCV and iron parameters, Bottom: Non responder in a patient with anaemia and bronchopneumonia and weekly Hb, CRP,MCV and iron parameters : Steady state iron parameters within 2-3 weeks; Hb response within 1-2 weeks.

In Table 2, for within group comparisons, C1, C2 and C3 subjects (serum FN >50 - 199 µg/L), a Hb response was observed to 90% of subjects. In C4, subjects (serum FN 200 to 299 µg/L), there was also an improvement but response was attenuated to 60%. One patient in the C5 (serum FN 300-399) µg/L responded to IV iron. There was no response for all C6 subjects (serum FN>400 µg/L).

Table 2 Response of IV iron in patients and haemoglobin with different ferritin concentrations.

Category	Age (yrs)	Hb g/dl	Hb 4/52 g/dl	Responders	CRP mg/L	MCV FL	Ferritin µg/L	TSAT %
C1 FN<50, µg/L n=14	78.4 ±10.1	9.3 ±0.8	12.5±0.8 ***	13(93)	30.2 ±31.2	83.1±8.2	27.7±9.2	7.6±3.9
C2 FN>50-100 µg/L n=20	83.3±8.0	8.7±0.1	11.2±1.2***	18(90)	44.6±38.6+	85.7±8.7	69.1± 16.9	10.1±4.1
C3 FN>100-199 µg/L n=17	84.1±8.1	9.0 ±0.1	11.1±1.4***	15(88)	67.9±44.7++	86.6±8.9	135.4±18.1	8.7±3.7
C4 FN>200-299 µg/L n=10	81.1±8.4	9.1 ±0.1	11.0 ±1.4**	6(60)	87.7±48.6+++	92.7±6.3	251± 24.0	9.0 ±3.2
C5 FN>300-399 µg/L n=3	80.0±5.7	9.6±0.5	11.1±0.4 ns	1(33)	56.0±22.1	90.0±1.4	363.0±0.82	10.7±4.5
C6 FN>400 µg/L n=21	84.3±7.6	9.9±0.9	10.4±0.1 ns	0(0)	113.8±86.0++++	91.9±4.7	664.7 ±296.2	10.6±4.8
Total n=85								

Data mean ± SD, parenthesis =percentage. Hb=haemoglobin, CRP=C-reactive protein, MCV=mean corpuscular volume, SAT=transferrin saturation

Hb response within group comparisons: paired student t-test : *** p<0001,**p=0.004,NS=not significant Paired student T test
Hb response for inter group response: unpaired student t-testing: C1vs C2 p=0.003 CI 4.5-20.1, C1 vs C3 p=0.01 CI 2.9-19.5, C1vs C4 p=0.004 CI 4.5-24.1
CRP between inter group: unpaired t test C1VC2 p=0.02 CI-49.0 to – 5.7, C1 Vs C3, p=0.01, CI -68.0 to -8.2, C1Vs C4, p=0.003, CI -93.7 to -22.6, C1Vs C6, p=0.0001, CI -132.1 to -47.5
++++p=0.0001. +++p=0.003, ++p=0.01, + p=0.02

For between groups comparisons, C1 subjects had a significantly greater improvement in Hb compared to C2, C3 and C4 subjects. CRP in C1 subjects was significantly less compared to C2, C3, C4 and C6. There were no significant difference in MCV between C1 and for C2-C6 subjects. C-reactive protein was significantly lower in C1 compared to C2 to C6 subjects.

Discussion

The ESC guidelines on heart failure with iron deficiency preceded bone marrow studies in patients with CAD. Nanas et al[13] evaluated marrow on 37 anaemic patients with heart failure of which 27 (73%) were iron deficient ID, mean age 57.9 ± years. Serum FN was significantly lower in the ID subjects although Hb was not significantly different between ID Vs non ID subject nor were MCV and CRP. Only serum iron SI was analyzed with no difference between the two cohorts. However, these are patients had end-stage disease with a significant mortality at three months.

Jawkowska et al[11] evaluated marrow in 31 subjects with stable CAD with ID Vs 34 subjects with CAD but without ID (mean age 63.0 ± 8 Vs 65.0 ± 8 years). The prevalence of ID was 48% there were no significant differences in mean Hb, MCV and CRP between the two cohorts. Serum ferritin was poorer surrogate maker on iron status compared to TSAT and SI. Boverborgh et al[12] examined 42 patients with CAD who underwent bone marrow before by pass (mean age 68.0 ± 9.7 years). The prevalence of ID was 40% n= 17 (mean age 68.8 ± 9.7). Although the ID group had significantly lower Hb: (mean Hb13.1 + 1.1 vs 14.6 + 1.1 g/dl) to non-ID group, subjects were not anaemic with no significant differences in the MCV and CRP. These studies suggest serum FN to be inferior to TSAT as surrogate markers on iron status.

The WHO criteria for anaemia is not practical to implement in the frail inpatient[2]. Our previous audit (169 females, mean age 84.7 years, 140 males, mean age 82.6 years): WHO criteria, captured 55% of females and nearly 70% of male patients. In our opinion, the rule of 10 (Hb <11g/dl) may be more practicable at 30% for both sexes.[14] A Hb rise of 1 g/dl can be considered to be significant with iron supplementation but a 2g/dl increase is more reliable.[15]

The WHO criterion for a low serum FN is <15µg/L for adults (clinical laboratories set at 10-20µg/L) [16]. Serum FN has a tendency to rise with age[5], very similar to erythrocyte sedimentation rate and CRP in healthy old individuals.[17,18] Guyatt et al examined marrow aspirates in 85 older community subjects with anaemia (males Hb <11 g/dl, females <12g/dl). A serum ferritin of <18 µg/L captured 55% (n=47) of subjects, at 45 µg/L, an additional 27% (n=23) to 82% and a FN to 100 µg/L (n=7), additional 10%. Ferritin needs to be reset at a higher level at 45 µg/L for older subjects. In the same study, a TSAT <20, captured 89% of subjects.[19]

Anaemia of inflammation and chronic disease is more prevalent than IDA in the older person.[8] These include a range of conditions: inflammatory arthritis, bowel disease, chronic infections/inflammation (e.g. tuberculosis, connective diseases) and malignancy. Ferritin is an acute phase reactant protein. ACD and IDA can be bedfellows or MA. These impose further restrictions on FN in its ability to define iron status

A large study om 2669 subjects >18 years old, (males Hb<13 and females Hb <11), where 50% of subjects had bone marrow assessments, Guyatt

proposed a serum FN at 40 µg/L for those with no inflammation and 70 µg/L for those with inflammatory conditions and ID.[20] Lipschitz evaluated bone marrow aspirates (designated absent, diminished, moderate and increased haemosiderin staining) and serum FN in 25 subjects with infection /inflammation against 27 controls. For each level of bone marrow iron content, it was observed that FN was three times higher in the inflammatory group against controls. In subjects with inflammation and absent/reduced hemosiderin, the upper value of FN was in the region of 200 µg/L.[21]

The iron transport apparatus also display deficiencies. TSAT (obtained as a ratio of SI and TIBC) is labile with diurnal variations over 24 hours and day to day[6,7] During infection/inflammatory states, TSAT is often reduced. Inflammation activate hepcidin and disrupts iron mobilization from the enterocyte to the circulation and iron from the reticulo-endothelial (RE) cell to the circulation resulting in a low TSAT or a functional iron deficiency (FID).[9]

Due to inherent deficiencies, assessment of iron status is best undertaken using several tests in parallel with two proposed models.[22] The MCV model utilizes MCV, TSAT and Zinc protoporphyrin (ZPP). However, ZPP is elevated in ID and AICD[23,24] and not available in most hospitals in the United Kingdom. The FN model utilizes FN, TSAT and ZPP. If any two are abnormal, then the subject has impaired iron status and a therapeutic trial of iron could be undertaken.

Oral iron supplementation has been undertaken over the past 50 years. However, side effects are common especially in the older person (70 per-cent with diarrhea or constipation).[25] This can be somewhat mitigated utilizing once a day instead of three times and more recently, alternate day oral supplementation.[26,27]

Unlike earlier iron formulations, current formulations have a very good safety profile and are used in (i) ID subjects who are intolerant to oral iron (ii) anaemia in certain disease states e.g. inflammatory bowel disease (IBD) where oral iron may exacerbate disease activity. Intravenous iron acts faster with a capacity to deliver a higher dose (1000mg per infusion Vs a maximum of 25 mg of oral elemental iron that can be absorbed per day.[28] Iron therapy by- passes "two blocks" (i) divalent metal transporter, for iron uptake from the bowel lumen onto the enterocyte and (ii) the enterocyte ferroportin block from enterocyte to the blood stream.[29, 30] There little role for oral iron during inflammation as the later activates hepcidin which "activate" the enterocyte and RE block limiting bowel absorption and iron transfer to the circulation.[31]

We initiated the current analysis using the ECS guidelines as our patient cohort are different (mean age 81.9 years) with multiple co-morbidities. Some may be too frail to undergo gastroenterological investigations. Furthermore, we encountered several clinicians initiating therapy based on a single abnormal biochemical entity.

All subjects in the current analysis had a raised CRP and reduced TSAT and the only variable was serum FN. There was a significant Hb response in C1, C2 and C3 (serum FN 50- to 199 µg/L). This is in agreement with bone marrow findings by Lipschitz[21] in anaemic subjects with inflammation. In C4 subjects (serum FN 200-299 µg/L), a response was also noted but was attenuated by 40%.

Category 1 (n=14, 17%) patients also displayed significantly greater improvement in Hb compared to C2, 3 and 4 patients. Category 1 were predominately ID with a significantly lower CRP compared to C2 to C6 subjects. In category 2, 3 and 4 (n=37, 44%) the anaemia is a MA (ACD and ID). Inflammatory cytokines such as interleukin 6 can affect erythropoiesis.[32] This may explain a subdued Hb response compared to IDA subjects in C1.

One patient in C5 had low STAT with a FN>300 µg/L and responded to iron. This patient had IBD, a group very likely to present with a MA. None of

the subjects in C6 (serum FN > 400 µg/L, n=21 or 25% of the analyzed cohort) responded even in the context of a low TSAT. These subjects had AICD.

A MCV of <70 Ft can be taken as strong evidence of ID provided thalassaemia is excluded [19]. Two subjects displayed an MCV<70Ft. One had thalassaemia and IDA with a modest Hb response (pre-Hb at 7.2g/dl to 9.4 g/dl post IV iron). The second patient had IDA. MCV lacks sensitivity as the typical microcytosis and hypochromic anaemia observed in ID can also be a feature in ACD.[33,34]

There was agreement with ESC. Guideline 1 refers to C1 and 2 (serum FN up to 100 µg/L). Guideline 2 refers to C3 and C4 subjects. There was some agreement although the Hb response in C4 (serum FN 200-299 µg/L) was attenuated. Therefore, the decision to give IV iron may need to rest with the treating clinician. For C5 subjects (serum FN 300-399 µg/L) the numbers were too small to make any firm conclusions. There was no response in C6 subjects (serum FN >400 µg/L, 25% of the study cohort). Clinicians should refrain from relying solely on a low TSAT to give IV iron.

Although IV iron infusions are relatively safe, it still needs to be administered in a facility with resuscitation facilities. There is a theoretical risk of exacerbation of infections when given in the context of a high CRP. (Historical data in patients with primary iron overload being more susceptible to certain bacterial infections).[35] A systematic review and met analysis on the safety and efficacy if IV iron revealed a modest reduction for the need for blood transfusion but a small increase of infection.[36]

There are cost implications £150 for each treatment and is the most common intravenous prescription in our hospital. Most cases require two infusions, given 1 week apart. Majority of the older subjects are not ambulatory, there are costs implications should they return for the second infusion. This can be mitigated by giving a single infusion (to treat the anaemia although may not fully replenish depleted iron stores). Single infusion has the advantage of reducing the risk of infusion reactions.

All subjects in the current analysis received Ferric carboxymaltose (FCM). Recent studies comparing FCM and Ferric derisomaltose (FDI) reveal similar efficacy and price but FDI may have a perceived advantage of reduced fatigue and hypophosphatemia.[37,38] The later may be due to the effect FCM on fibroblast growth factor 23.[39] However, the long term consequences remain uncertain.

This was retrospective study. As such, several parameters were not available. Sixteen subjects did not have a post Hb. On review, eight had a ferritin of <50 µg/L and four with the ferritin >400 µg/L. Therefore, it is very unlikely to affect the conclusion. It may be useful to repeat the analysis in a different hospital, explore the FN between 301-399 µg/L and evaluate alternative parameters e.g. soluble serum transferrin receptor(sTfR)[40] and reticulocyte Hb level [41] which may aid identification of anaemic subjects who will respond to iron.

Conclusion

ESC can be utilized to help predict response to IV iron, a TSAT < 20, in tandem with an elevated CRP with a serum FN <199 µg/L. A serum FN between 200 to 299 µg/L, the response is less optimal so the decision should rest with the treating clinician There is little role for IV iron with a serum FN beyond 400 µg/L even in the on context of a very low TSAT. MA is relatively common where their response may be less optimal compared to IDA.

Conflict of Interest:

The authors have no conflicts of interest to declare.

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