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Original article

Anemia management and transfusion strategy in internal medicine units: Less is more

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ABSTRACT

Blood transfusion is one of the most overused procedures, especially in elderly patients. Despite the current transfusion guidelines recommending a restrictive transfusion strategy in stable patients, the clinical practice varies according to physicians' experience and implementation of patient blood management. This study aimed to evaluate the anemia management and transfusion strategy in anemic elderly hospitalized and the impact of an educational program.

We enrolled ≥ 65-year-old patients who presented or developed anemia during admission to a tertiary hospital's internal medicine and geriatric units. Patients with onco-hematological disorders, hemoglobinopathies and active bleeding were excluded. In the first phase, anemia management was monitored. In the second phase, the six participating units were divided into two groups and two arms: Educational (Edu) and non-educational (NE). During this phase, physicians in the Edu arm underwent an educational program for the appropriate use of transfusion and anemia management. In the third phase, anemia management was monitored.

Comorbidities, demographic and hematological characteristics were similar in all phases and arms. The percentages of transfused patients during phase 1 were 27.7% in NE and 18.5% in the Edu arm. During phase 3, it decreased to 21.4% in the NE and 13.6% in the Edu arm. Hemoglobin levels at discharge and after 30 days were higher in the Edu group despite reduced use of blood transfusion.

In conclusion, a more restrictive strategy was comparable or superior to the more liberal one in terms of clinical outcomes, with the advantage of saving red blood cell units and reducing related side effects.

1. Introduction

Anemia is a global public health problem affecting subjects of all ages and gender, with significant consequences for human health and an impact on social and economic aspects. The aging of the population unveils the burden of anemia in the elderly, defined as individuals aged 65 years and above. In this group, anemia is mainly of a mild degree [1,2] and increases with age [1]. Its prevalence in community-dwelling subjects aged >65 is around 11%, with variability across ages and ethnicities [1,3]. The prevalence dramatically increases in patients

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hospitalized for any reason, ranging between 48% to 60% [4,5]. Anemia contributes to morbidity, including decreased physical performance, increased risk of falls, frailty, dementia, hospitalization, and mortality [6,7].

With advancing age, many factors can contribute to the onset of anemia, and the etiology is often multifactorial [3,8]; 1/3 is due to nutrient deficiency, 1/3 to inflammation, and 1/3 remains unexplained. Anemia treatment requires, as the first step, whenever possible, the correction of any underlying cause [9]. Under this scenario, red blood cell (RBC) transfusion should be limited to patients with severe anemia, those with cardiovascular disease or specific clinical symptoms, and those without other treatment options. The Choosing Wisely campaign of the AABB (formerly the American Association of Blood Banks) states not to transfuse RBC for iron deficiency without hemodynamic instability [10]. The current RBC transfusion guidelines by the AABB recommend a restrictive transfusion strategy, with hemoglobin (Hb) thresholds of less than 7 g/dL in hospitalized stable patients and less than 8 g/dL in those with coexisting cardiovascular disease and undergoing cardiac or orthopedic surgery [11].

Restrictive strategies have consistently resulted in the same or improved outcomes compared to liberal transfusion strategies (Hb threshold, <10 g/dL). Moreover, the restrictive approach resulted in a 43% reduction in patients who received a transfusion [12]. However, it is common malpractice to over-transfuse older patients, causing an increased risk for the individual, useless costs for public health and reduced availability of blood for those who may need it. Indeed, blood transfusion is the most common procedure performed during inpatient hospitalizations [13] and one of the top 5 overused procedures, with most units transfused in older patients [11].

Embracing evidence-based transfusion guidelines reduces risks and costs while improving outcomes, thus increasing the value of care provided [13]. However, clinical practice varies according to physicians' experience and the local implementation of patient blood management (PBM) programs. PBM education programs have been proven to reduce the number of RBC units transfused, especially in the peri-surgical and gynecology setting [14,15]; yet, they are still far from being implemented as the standard of care, particularly in the elderly, due to the lack of awareness among health professional figures.

The aim of the study was to evaluate anemia management and the impact of an educational program in internal medicine and geriatric units of an academic hospital in an Italian metropolitan area.

2. Materials and methods

2.1. Study design and setting

An interventional non-pharmacological study was conducted between the 1st of June 2018 and the 30th of September 2019 at Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan; in six internal medicine and geriatric units, we investigated the anemia management and transfusion strategy in anemic elderly patients to evaluate the impact of an educational program. The six participating units were divided into two groups, each including three units, based on location in the hospital and shift organization to avoid overlaps in the physicians and nurse allocation. Then, the two groups were randomized into two different arms using a coin: one group received an educational program and the other group did not receive it. In order to minimize the bias related to extraneous/spontaneous factors (historical and cultural reasons) on the reduction of RBC transfusions, we randomized the two groups after the first observational phase (Fig. 1).

The study includes (Fig. 1):

- Phase 1: observational phase.
- Randomization. The six participating units were divided into two arms and randomized to:

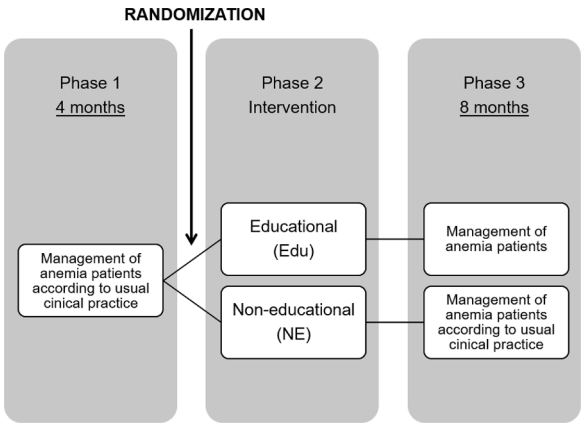

Fig. 1. Study phases.
Phase 1: observational phase before education; Phase 2: intervention phase; Phase 3: Post-intervention observational phase; Edu: Educational arm; NE: Non-educational arm.

  i) Educational arm (Edu)
  ii) Non-educational arm (NE)

- Phase 2: intervention phase: all the physicians, including residents, randomized to the Edu arm, were involved in an educational program (see intervention paragraph). Those randomized to the NE did not receive any educational program.
- Phase 3: Post-intervention observational phase.

We performed an observational phase of 4 months and a post-intervention phase of 8 months (Fig. 1) to avoid insufficient enrollment based on our previous study in which 1/3 of the hospitalized anemic patients received RBC transfusions [4] and a Cochrane systematic review that concluded that a restrictive strategy resulted in a 43% reduction in the proportion of patients who received a transfusion [12].

2.2. Patients

Patients aged 65 years or older admitted to internal medicine and geriatric units of Fondazione IRCCS Ca' Granda Policlinico, Milano, who fulfilled the inclusion and exclusion criteria, were evaluated for transfusion strategy.

The inclusion criteria were: age ≥ 65 years and presence of anemia, defined as Hb levels <12 g/dl in women and <13 g/dl in men, at any moment of the hospital stay during the enrolment period. Exclusion criteria were: hemodynamic instability due to suspected or confirmed active bleeding, terminal state, hematological malignancies and hemoglobinopathies. The transfusion strategy was evaluated in the entire admitted population based on data from the blood bank. In a subset of patients, who were consecutively enrolled and signed the informed consent, we evaluated demographic, hematological, biochemical, and clinical data at enrollment, discharge, and a 30-day follow-up after discharge to analyze the anemia management.

2.3. Outcomes

The primary outcome was the anemia management and transfusion strategy in all anemic elderly subjects hospitalized in internal medicine and geriatric units.

The secondary outcome was the evaluation of change in the proportion of anemic subjects that received RBC transfusion in the Educational arm compared to the Non-Educational arm.

2.4. Intervention

During the intervention phase, all the physicians of the units randomized to the Edu arm participated in the educational program. The educational program consisted of a 3-hour lesson on the diagnosis of anemia, the treatments of the underlying causes and the use of IV iron, the most recent guidelines on blood transfusion (recommendations, adverse reactions, risks/benefit balance, and costs) with a focus on the elderly and frail patients. Fig. 2 shows a proposed approach to elderly anemic patients in internal medicine and the geriatric ward, according to good clinical practice. Graphical material representing Fig. 2 and transfusion guidelines were affixed in different places of the internal medicine and the geriatric units that underwent the educational program.

2.4. Statistical analysis

We used linear regression models to analyze quantitative variables (ln-transformed when necessary). To analyze categorical variables, we fitted Poisson regression models with robust standard error (an alternative to log-binomial regression, which often has convergence problems) [16]. To evaluate changes from Phase 1 to Phase 3 in the two arms Edu and NE, we included in the model the covariates: arm, phase, and their interaction (product-term). Statistical analyses were performed with Stata 17 (StataCorp. 2021).

The study was approved by the ethical review committee "Comitato Etico Milano Area 2″ (Protocol number 322_2018bis) and was carried out in compliance with the principles established in the Helsinki Declaration.

3. RESULTS

3.1. Patients' characteristics and prevalence of anemia in internal medicine and geriatric units

Among the 1412 hospitalized patients admitted to the internal medicine and geriatric wards between the 1st of June and the 30th of September 2018 (Phase 1) (Fig. 3), 1082 were aged ≥= 65 years. To estimate the number of anemic patients, we randomly chose three of the six participating wards and evaluated the prevalence of anemia in the admitted subjects ≥=65 years. The prevalence of anemia was 59.6 ± 4.3% and 589 patients were included in the study (Fig. 3).

In the post-education phase (Phase 3), between the 1st of February 2019 and the 30th of September 2019, among the 3251 hospitalized patients admitted to the internal medicine and geriatric wards, 2535 were aged ≥= 65 years, and 1429 were included in the study (Fig. 3).

For most variables, we did not observe any difference between the two branches and between Phase 1 and Phase 3, except for solid cancer prevalence that was higher in the Edu branch during Phase 1, compared to all the other groups (Table 1).

3.2. Anemia is not always perceived as a clinical problem

At admission, anemia was mild to moderate and normochromic normocytic on average. (Table 2). We did not observe significant differences in hematological and biochemical parameters between the two branches from Phase 1 to Phase 3. We only observed a difference in ferritin concentration at admission in the Edu branch between the two phases.

Interestingly, the diagnostic laboratory workup for anemia was performed only in a proportion of enrolled patients. Folate and B12 were evaluated in about two-thirds of patients in both phases and branches, while iron and hemolysis parameters were measured in 70% of subjects. No differences in the diagnostic approach in terms of laboratory tests to diagnose nutritional deficiencies were observed between the pre-and post-education phases in the Edu group (Table 2). Furthermore, endoscopic investigations were performed in one-fifth of the patients.

3.3. Transfusion strategy

We evaluated the transfusion strategy in the entire population admitted during the study periods. During Phase 1, the proportion of transfused anemic patients was 136/589 (23.1%), with 27.7% (81/292) in the NE group and 18.5% (55/297) in the Edu group.

In Phase 3, the proportion of transfused anemic patients decreased in both groups, with 21.4% (158/740) of transfused subjects in the NE group and 13.6% (94/689) in the Edu group.

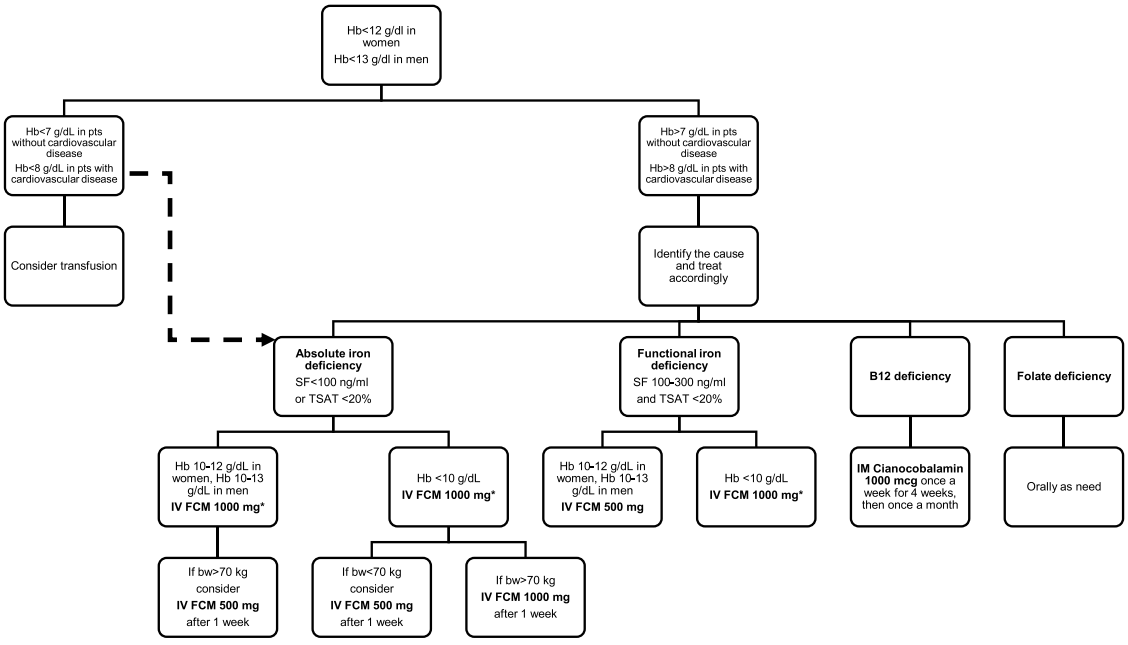

Fig. 2. The proposed approach to anemic stable hospitalized elderly patients.
Hb: hemoglobin; pts: patients; BW: body weight; TSAT: transferrin saturation; ID: iron deficiency; SF: serum ferritin; FCM: ferric carboxymaltose; IV: intravenous; IM: intramuscular. *If body weight<35 kg, the dose will be 20 mg iron/kg body weight.

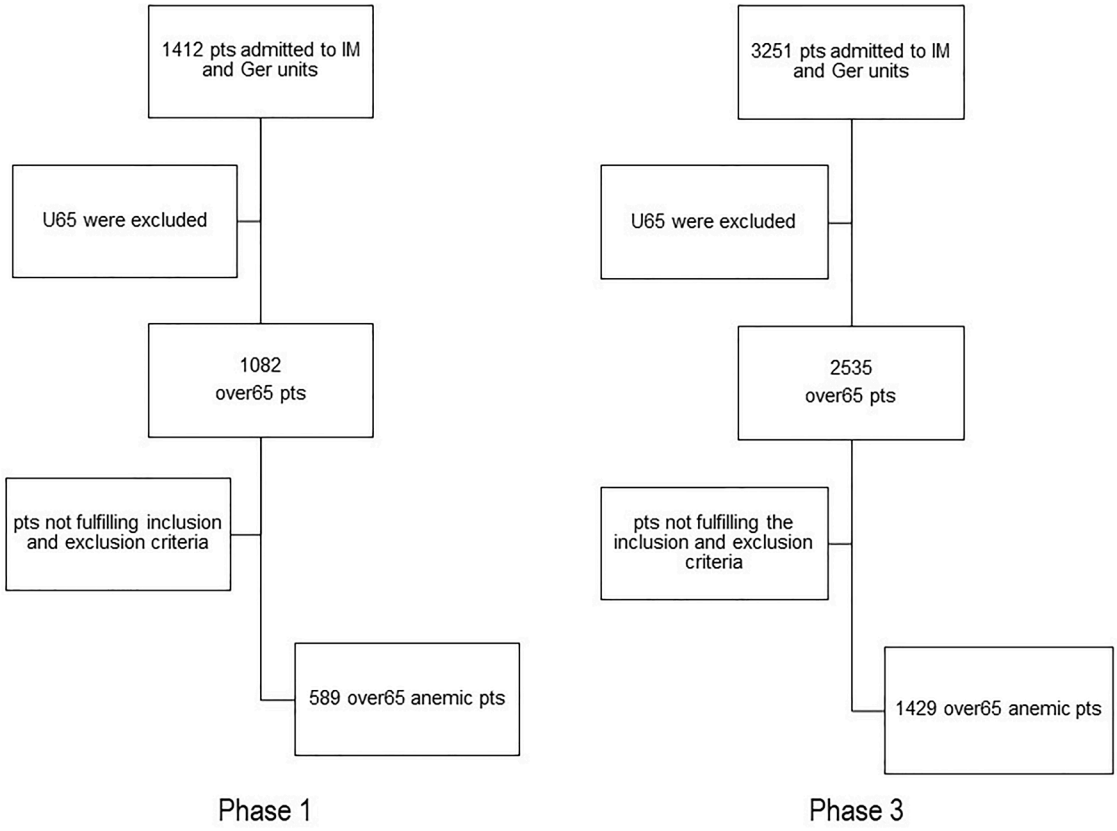

Fig. 3. Study population divided into pre- (Phase 1) and post-intervention (Phase 3).
IM: internal medicine; Ger: geriatric; pts: patients; U65: aged under 65; Phase 1: observational phase before education; Phase 3: Post-intervention observational phase.

Table 1
Demographic and clinical characteristics at the admission.

Demographic and clinical characteristic	Phase 1		Phase 3		p - interaction
	Branch NE	Branch Edu	Branch NE	Branch Edu	
Patients, no.	81	67	116	119	
Sex, Female, n (%)	44 (54)	35 (52)	46 (44)	57 (49)	p 0.57
Age (yr), mean ± SD (median)	80 ± 8 (82)	82 ± 7 (83)	82 ± 8 (83)	83 ± 8 (82)	p 0.63
Solid cancer, n (%)	22/81 (27)	41/67 (61)	40/116 (34)	38/119 (32)	p 0.01
Diabetes, n (%)	22/81 (27)	18/67 (27)	42/116 (36)	48/119 (40)	p 0.73
CAD, n (%)	35/81 (43)	26/67 (39)	31/116 (27)	42/119 (35)	p 0.21
CHF, n (%)	25/81 (31)	35/67 (52)	23/116 (20)	37/119 (31)	p 0.83
CKD, n (%)	25/81 (31)	22/67 (33)	52/116 (45)	69/119 (58)	p 0.52
Folate deficiencies, n (%)	25/51 (49)	18/41 (44)	23/76 (30)	30/85 (35)	p 0.41
B12 deficiencies, n (%)	7/53 (13)	7/41 (17)	2/79 (3)	8/85 (9)	p 0.25
Hypothyroidism, n (%)	8/44 (18)	4/56 (7)	12/65 (18)	10/115 (9)	p 0.80

CAD: Coronary artery disease; CHF: Congestive heart failure; CKD: Chronic kidney disease; Phase 1: observational phase before education; Phase 3: Post-intervention observational phase; Edu: Educational arm; NE: Non-educational arm; SD: standard deviation.

Therefore, a similar reduction between the two branches was observed (−6.4% in NE and −4.8% in Edu Branch, p-interaction: 0.82) (Fig. 4).

3.4. Complications, mortality, and therapy

Complications during hospitalization, mortality rate, and treatment for anemia, divided into branches and phases, are summarized in Table 3. We did not see significant changes between the two groups over time, except for the infection rate in the NE arm between the two phases.

3.5. Clinical outcome, characteristics at discharge and at 30-day follow-up

We observed an increase in hospitalization length between the two phases for both the NE and the Edu arm; no differences between arms were found when adjusted for age and gender. At discharge, patients still presented mild to moderate normochromic and normocytic anemia with values similar to admission (Table 4).

We performed a phone call 30 days after discharge to investigate the patients' status, and possible re-hospitalization and to collect data about a hematological follow-up. We obtained data from about half of the enrolled patients discharged from the internal medicine and geriatric units (Table 5). From Phase 1 to Phase 3, hemoglobin levels 30 days after discharge increased in the Edu group and decreased in the NE group (Table 5).

4. Discussion

Although anemia represents a significant health problem determining disability [17] with more than one-third of the world population

Table 2
Laboratory characteristics at the admission.

Laboratory parameters	Phase 1		Phase 3		p - interaction
	Branch NE	Branch Edu	Branch NE	Branch Edu	
WBC /mm3, mean ± SD; (median)	8967 ± 3215 (8500)	9156 ± 4707 (7850)	9633 ± 5866 (8450)	8786 ± 4102 (7890)	p 0.29
RBC 106/mm3, mean ± SD; (median)	3.70 ± 0.70 (3.75)	3.73 ± 0.70 (3.77)	3.59 ± 0.64 (3.54)	3.58 ± 0.58 (3.60)	p 0.78
Hb g/dl, mean ± SD; (median)	10.3 ± 1.7 (10.6)	10.5 ± 1.5 (10.8)	10.1 ± 1.5 (10.4)	10.2 ± 1.4 (10.4)	p 0.98
MCV fl, mean ± SD; (median)	85.1 ± 9.5 (87.0)	85.7 ± 10.4 (85.7)	84.5 ± 8.8 (85.7)	89.9 ± 10.3 (87.6)	p 0.36
RDW%, mean ± SD; (median)	16.1 ± 4.3 (15.0)	15.7 ± 2.4 (15.4)	15.85 ± 2.6 (15.0)	15.6 ± 2.5 (14.9)	p 0.32
PLT 103/mm3, mean ± SD; (median)	226 ± 125 (209)	239 ± 126 (211)	228 ± 106 (211)	237 ± 121 (226)	p 0.91
Ferritin µg/L, mean ± SD; (median)	833 ± 4084 (182)	521 ± 938 (174)	367 ± 340 (293)	315 ± 305 (195)	p 0.57
Transferrin mg/dL, mean ± SD; (median)	201 ± 58 (196)	191 ± 67 (184)	181 ± 56 (171)	192 ± 58 (188)	p 0.17
Iron µg/dL, mean ± SD; (median)	50 ± 38 (41)	46 ± 36 (33)	44 ± 43 (36)	48 ± 42 (34)	p 0.37
LDH UI/dL, mean ± SD; (median)	272 ± 409 (200)	270 ± 398 (208)	222 ± 111 (204)	235 ± 210 (210)	p 0.80
Bilirubin mg/dL, mean ± SD; (median)	1.08 ± 2.00 (0.55)	0.76 ± 0.71 (0.54)	0.99 ± 1.72 (0.53)	0.82 ± 1.23 (0.52)	p 0.64
CRP mg/L, mean ± SD; (median)	6.41 ± 7.50 (3.45)	7.53 ± 8.23 (3.74)	7.50 ± 8.73 (4.31)	7.28 ± 8.27 (3.84)	p 0.44
Creatinine mg/dL, mean ± SD; (median)	1.28 ± 0.74 (1.05)	1.25 ± 0.82 (1.02)	1.44 ± 1.09 (1.15)	1.43 ± 0.97 (1.19)	p 0.92

WBC: White Blood Cells; RBC: Red Blood Cells; Hb: Hemoglobin; MCV: mean corpuscular volume; RDW: Red cell distribution width; PLT: Platelet; LDH: Lactate dehydrogenase; CRP: C-reactive protein; Phase 1: observational phase before education; Phase 3: Post-intervention observational phase; Edu: Educational arm; NE: Non-educational arm; SD: standard deviation.

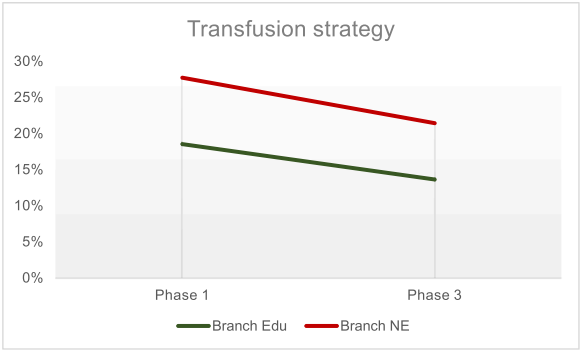

Fig. 4. Transfusion strategy between two phases in different branches. Phase 1: observational phase before education; Phase 3: Post-intervention observational phase; Edu: Educational arm; NE: Non-educational arm.

affected [18], it does not receive its requisite attention in many public health spheres[19]. As suggested by Kassebaum, "such inattention may be partly because anemia is thought of as a by-product of other disease

Table 3
Complications, mortality and therapy during hospitalization.

Characteristic	Phase 1		Phase 3		p - interaction
	Branch NE	Branch Edu	Branch NE	Branch Edu	
Complications					
Infection, no. (%)	35/81 (43)	34/67 (51)	68/116 (59)	75/118 (64)	p 0.67
Stroke, no. (%)	0/81 (0)	1/67 (1)	4/116 (3)	2/118 (2)	NC
ACS, no. (%)	1/81 (1)	1/67 (1)	4/116 (3)	2/118 (2)	p 0.66
DVT, no. (%)	3/81 (4)	5/67 (7)	1/116 (1)	1/117 (1)	p 0.64
PE, no. (%)	4/81 (5)	6/67 (9)	2/116 (2)	4/118 (3)	p 0.94
Mortality					
Death during hospitalization, no. (%)	1/81 (1)	1/67 (1)	1/116 (1)	2/119 (2)	p 0.75
Therapy					
Oral iron, no. (%)	12/80 (15)	6/66 (9)	8/116 (7)	5/118 (4)	p 0.90
IV iron, no. (%)	19/80 (24)	8/67 (12)	30/116 (26)	26/118 (22)	p 0.26
One unit policy, no. (%)	27/32 (84)	5/8 (63)	25/32 (78)	13/17 (76)	p 0.39
B12 therapy, no. (%)	13/80 (16)	10/67 (15)	11/116 (9)	10/118 (8)	p 0.99
Folate therapy, no. (%)	36/81 (44)	22/67 (33)	44/116 (28)	32/118 (27)	p 0.96
ESA therapy, no. (%)	0/73 (0)	2/64 (3)	5/116 (4)	3/118 (3)	NC

ACS: Acute coronary syndrome; DVT: Deep vein thrombosis; PE: pulmonary embolism; IV: intravenous; ESA: Erythropoiesis Stimulating Agents; Phase 1: observational phase before education; Phase 3: Post-intervention observational phase; Edu: Educational arm; NE: Non-educational arm; NC: not calculable due to sparse data.

Table 4
Characteristics at discharge and average hospitalization.

Characteristic	Phase 1		Phase 3		p - interaction
	Branch NE	Branch Edu	Branch NE	Branch Edu	
Hospitalization (day), mean ± SD; (median)	13 ± 10 (10)	10 ± 7 (8)	14 ± 11 (12)	12 ± 6 (10)	p 0.81
WBC /mm3, mean ± SD; (median)	7295 ± 2448 (7130)	7534 ± 2652 (7510)	7673 ± 2986 (7090)	7591 ± 3193 (7040)	p 0.62
RBC 106/mm3, mean ± SD; (median)	3.72 ± 0.66 (3.61)	3.82 ± 0.68 (3.83)	3.64 ± 0.56 (3.57)	3.60 ± 0.60 (3.56)	p 0.23
Hb g/dl, mean ± SD; (median)	10.7 ± 1.5 (10.5)	10.8 ± 1.5 (10.8)	10.3 ± 1.3 (10.1)	10.3 ± 1.3 (10.3)	p 0.81
MCV fl, mean ± SD; (median)	86.7 ± 7.7 (88.0)	86.8 ± 9.8 (86.6)	85.3 ± 8.6 (86.2)	87.4 ± 8.9 (88.4)	p 0.23
RDW%, mean ± SD; (median)	16.9 ± 4.8 (16.0)	15.9 ± 2.6 (15.4)	16.0 ± 3.0 (15.4)	16.3 ± 3.3 (15.4)	p 0.09
PLT 103/mm3, mean ± SD; (median)	249 ± 116 (245)	278 ± 131 (250)	274 ± 115 (259)	273 ± 119 (256)	p 0.20

WBC: White Blood Cells; RBC: Red Blood Cells; Hb: Hemoglobin; MCV: mean corpuscular volume; RDW: Red cell distribution width; PLT: Platelet; Phase 1: observational phase before education; Phase 3: Post-intervention observational phase; Edu: Educational arm; NE: Non-educational arm; SD: standard deviation.

Table 5
Complete blood count and 30-day outcome.

30-days follow-up	Phase 1		Phase 3		p - interaction
	Branch NE	Branch Edu	Branch NE	Branch Edu	
Death rate, no. (%)	3 (4)	3 (4)	8 (7)	4 (3)	p 0.36
Complete blood count					
	n *= 54	**n *= 30**	**n *= 57**	**n *= 59**	
WBC /mm3, mean ± SD; (median)	7265 ± 2548 (6635)	7384 ± 3060 (7070)	6955 ± 3029 (6700)	7994 ± 3912 (6390)	p 0.34
RBC 106/ mm3, mean ± SD; (median)	3.94 ± 0.70 (3.92)	4.02 ± 0.69 (3.92)	3.79± 0.61 (3.76)	3.92 ± 0.59 (3.90)	p 0.58
Hb g/dl, mean ± SD; (median)	11.3 ± 1.7 (11.2)	11.0 ± 1.3 (11.2)	10.8 ± 1.6 (10.8)	11.5 ± 1.6 (11.2)	p 0.03
MCV fl, mean ± SD; (median)	87.5 ± 9.6 (88.0)	84.8 ± 8.9 (86.1)	87.2 ± 9 (87.1)	88.8 ± 7.5 (88.4)	p 0.08
RDW%, mean ± SD; (median)	16.6 ± 3.1 (16.0)	16.4 ± 2.9 (15.8)	16.6 ± 3.0 (15.9)	16.2 ± 2.9 (15.5)	p 0.84
PLT 103/ mm3, mean ± SD; (median)	221 ± 92 (217)	253 ± 100 (251)	252 ± 108 (234)	253 ± 109 (232)	p 0.30

WBC: White Blood Cells; RBC: Red Blood Cells; Hb: Hemoglobin; MCV: mean corpuscular volume; RDW: Red cell distribution width; PLT: Platelet; Phase 1: observational phase before education; Phase 3: Post-intervention observational phase; Edu: Educational arm; NE: Non-educational arm; SD: standard deviation.
* The number of patients discharged from internal medicine and geriatrics units for which we obtained data at 30 days.

processes rather than as a target for intervention in and of itself' [20]. This seems more relevant to the elderly. Indeed, published data mainly focus on anemia prevalence and its consequences. In contrast, there is little data about anemia management in internal medicine wards [5, 21–23].

In our study, we observed a prevalence of anemia in elderly hospitalized patients around 60%. These findings are consistent with previous studies, confirming that anemia is a major health problem [4,5,21–23]. Regarding anemia evaluation and etiology identification, we observed that approximately two-thirds of the patients underwent lab tests to define the type of anemia, which is essential to establishing a proper treatment. We herein propose a diagnostic and treatment approach (Fig. 2) that includes the most frequent causes of anemia in stable hospitalized elderly patients, namely nutritional deficiency (iron, vitamin B12, and folate) and anemia of inflammation (functional iron deficiency). Of note, we captured that further tests, including endoscopic exams, were performed in an even lower percentage of patients. On the one hand, this could be related to the benefit-risk ratio in a fragile population. While on the other hand, it supports the hypothesis that anemia does not receive enough attention. Incomplete comprehension of the underlying cause of anemia could lead to inappropriate treatments, especially RBC transfusion. Indeed, according to the World Health Organization (WHO), in 2016 [24], up to 79% of RBC units were transfused in patients older than 60 years.

PBM programs have been extensively implemented in peri-surgical and gynecology settings, while no data are available in the internal medicine and geriatric context. In 2021 the WHO included the elderly and those with hospital-acquired anemia among the populations that could benefit from PBM ([25]). The PBM program by the WHO underlines the importance of creating awareness and includes three pillars: i) detection and management of anemia and iron deficiency, ii) minimization of blood loss and optimization of coagulation and iii) leveraging and optimizing the patient specific physiological tolerance of anemia. Our educational program, which was conducted before 2021, aimed at increasing awareness and, except for the second pillar that is more for surgical populations, it focused on treatments alternative to transfusion, especially in the presence of iron deficiency (Fig. 2) and the importance of evaluating every single patient according to clinical and not only laboratory data. Indeed, elderly patients hospitalized in internal medicine and geriatric units are complex, and we believe that a broad and integrated approach should be implemented. This is the first study that evaluates the implementation of a strategy to increase awareness among physicians in internal medicine and geriatric units.

Our educational program was based on three hours of lectures and discussions on frontal lessons by experts in the field. Educational material remained available in physicians' offices to be consulted during daily practice. However, we did not observe any significant difference in the diagnostic approach to anemia between those educated and those not educated. Considering the transfusion approach, remarkably, the non-educated group had a higher transfusion rate than the educated one at baseline (27.7% of anemic patients vs. 18.8%) even though patients admitted in the two arms did not differ for hematological parameters (including Hb levels) nor the majority of comorbidities. Given that, we explored potential differences in physicians' characteristics. We observed that the mean age of doctors in the non-educated group was higher than in the educated group (data not shown). This could be related to a different awareness of PBM programs and that the youngest colleagues are more prone to restrictive transfusion strategies given the diffusion of the Less is more Campaign in medical school. Based on recent evidence, implementing these approaches should be a pillar of medical school and Continuing Medical Education (CME) courses since blood administration is often not perceived as a treatment with potential side effects [26,27] and as a limited resource, as clearly exacerbated by the pandemic.

Interestingly, we observed a reduction in the percentage of transfused patients in both Non-educated and Educated groups. This global reduction could be related to the Hawthorne effect; it is possible that doctors modified their approach as a consequence of being observed. The observed transfusion reduction was similar (~5%) in the two arms. Although we expected a more significant decrease in the Edu than the NE, considering the baseline, the reduction proportion was higher in the Edu group, which reached a transfusion rate of only 13% of anemic elderly patients.

We acknowledge that the educational program might have had some limitations regarding time and strength to modify the daily clinical practice. However, this was the best strategy we could provide, given the limited time of physicians due to their clinical duties. With this in mind, we think our approach should be combined with more strict and practical strategies in the RBC unit request phase through questions that evaluate the appropriateness of the transfusions according to the evidence.

Despite the different percentages of transfused anemic patients in the two arms, these different strategies did not impact the mortality rate. Moreover, hemoglobin values at discharge were similar in all the groups, but we observed a decrease in hemoglobin concentration in the NE branch and an increase in the Edu branch 30 days after discharge. Such a difference could be related to implementing cause-specific treatments as an alternative to RBC transfusion. Our data suggest that a more restrictive strategy, as the one applied in the Edu group, did not negatively affect clinical outcomes or even improved them (i.e., Hb levels at 30 days after discharge) while saving RBC units.

The limitations of our study are that we collected data on the management of anemia only in a subgroup of patients. Furthermore, data at 30 days were available in half of the enrolled patients.

In conclusion, our study confirms that anemia is a major health

problem in the elderly. Regarding its management, a restrictive transfusional approach was comparable or superior to the more liberal one in terms of clinical outcomes. Moreover, with this approach, unnecessary RBC units were saved, and potential transfusion-related side effects were prevented. Education remains a pillar in improving anemia diagnosis and management; however, weaning doctors off their love affair with blood remains a major challenge.

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Declaration of Competing Interest

MDC has been or is a current consultant for Vifor Pharma. The other authors have no conflict of interest related to this research.

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