Léčebné užití železa na ICU

OA Dr. Stibor B.

ICU, Landesklinikum Baden bei Wien, Austria

no conflict of interest

OA Dr. Stibor B.

ICU, Landesklinikum Baden bei Wien, Austria

přehled

1. anémie na ICU
2. nedostatek železa
3. železo a infekce
4. *hepcidin*
5. jak substituovat?
6. Landesklinikum Baden bei Wien

anémie
na ICU

Anemia Frequency

>60% of ICU patients upon admission
90% of ICU patients by day 3 in ICU
97% of ICU patients by day 8

Thomas J, Jensen L, Nahirniak S, Gibney RT. Anemia and blood transfusion practices in the critically ill: a prospective cohort review. Heart Lung. 2010;39(3):217-225.

Laborübersicht

10.01.2020 21:43 - 17.01.2020 21:43

Variablen \ Zeit	13.01.20 17:12	14.01.20 05:36	15.01.20 05:45	16.01.20 05:39	17.01.20 07:00
Blutbild visite					
Leukozyten 3.6-10.2[G/l]	28.6	25.6	23.2	21.0	25.2
Erythrozyten 4.3-5.15[T/l]	3.84	3.62	3.47	3.42	3.16
Hämoglobin 13.5-15.4[g/dl]	12.1	11.3	10.9	10.7	10.0
Hämatokrit 39.5-45.5[%]	36.8	34.6	33.5	32.6	30.6
Thrombozyten 160-370[G/l]	292	290	297	275	207
Elektrolyte					
Serumnatrium 136-145[mmol/l]	137	138	139	141	150
Serumkalium 3.5-5.3[mmol/l]	5.3	5.4	4.9	4.0	4.4
Chlorid 98-107[mmol/l]	104	102	102	102	105
Serum Kalzium 2.2-2.7[mmol/l]	2.28	2.28	2.24	2.15	2.42
Magnesium 0.66-0.99[mmol/l]	1.12	1.07	1.07	0.93	0.85
Phosphor 0.81-1.45[mmol/l]	2.15	1.98	1.33	1.19	0.72

Laborübersicht

08.01.2020 11:53 - 15.01.2020 11:53

Zeit / Variablen	09.01.20 05:53	10.01.20 05:42	11.01.20 05:43	12.01.20 05:51	13.01.20 05:38	14.01.20 05:36	15.01.20 05:45
Blutbild visite							
Leukozyten 3.6-10.2[G/l]	28.1	19.1	13.0	11.7	10.5	9.7	9.4
Erythrozyten 4.3-5.15[T/l]	3.31	3.13	3.24	3.32	3.21	3.22	3.26
Hämoglobin 13.5-15.4[g/dl]	8.9	8.3	8.7	8.9	8.5	8.5	8.7
Hämatokrit 39.5-45.5[%]	27.7	26.8	28.0	28.8	27.7	27.0	27.7
Thrombozyten 160-370[G/l]	191	182	168	178	171	178	214
Elektrolyte							
Serumnatrium 136-145[mmol/l]	144	151	153	147	142	143	140
Serumkalium 3.5-5.3[mmol/l]	4.4	4.1	5.2	4.3	4.0	4.5	4.3
Chlorid 98-107[mmol/l]	96	103	109	108	105	104	102
Serum Kalzium 2.2-2.7[mmol/l]	2.16	2.10	2.35	2.33	2.21	2.21	2.28
Magnesium 0.66-0.99[mmol/l]	0.93	0.93	0.91	0.80	0.79	0.82	0.87
Phosphor 0.81-1.45[mmol/l]	1.93	1.23	1.04	0.92	1.43	1.30	1.38

příčiny?

- *multifaktoriální*
- akutní/chronický **zánět**
- uvolnění **hepcidinu**, cytokinů
- manifestní/okultní **krvácení**
- snížená produkce **erytropoetinu**
- časté/nadměrné **krevní odběry** (iatrogenní)
- hemolýza u **extrakorporálních** metod
- …

Meybohm. Intensivmedizin up2date 2017; 13 (3): 291–307

iatrogenní anémie na ICU

- krevní objem u dospělých: cca **70-80** ml/kg
- cca **5** litrů u 70 kg pacienta
- životnost erytrocytů cca **120** dní
- kostní dřeň produkuje denně cca 1% objemu krve (asi **50ml**)
- diagnostické krevní odběry až **70 ml/d** (500 ml/týden)
- odhaduje se, že **39-44% ICU** pacientů dostanou alespoň **1 EBR** kvůli krevním odběrům

Corwin, Crit Care Med 2004;32:39-52

RESEARCH ARTICLE

A Simple "Blood-Saving Bundle" Reduces Diagnostic Blood Loss and the Transfusion Rate in Mechanically Ventilated Patients

Reimer Riessen[1]*, Melanie Behmenburg[1], Gunnar Blumenstock[2], Doris Guenon[2], Sigrid Enkel[3], Richard Schäfer[4], Michael Haap[1]

1 Department of Internal Medicine, Medical Intensive Care Unit, University of Tübingen, Tübingen, Germany, **2** Department of Clinical Epidemiology and Applied Biometry, University of Tübingen, Tübingen, Germany, **3** Clinical Transfusion Medicine, University of Tübingen, Tübingen, Germany, **4** Institute for Transfusion Medicine and Immunohaematology, German Red Cross Blood Donor Service Baden-Württemberg-Hessen GmbH, Johann-Wolfgang-Goethe-University Hospital, Frankfurt/Main, Germany

Riessen, PloS One 2015;10:e0138879

prevence:

- „bundle“
- uzavřený arteriální systém
- individualizace odběrů
- minimalizace odběrů
- 1 ml pro Astrup; 2,7 ml (místo 5,5 ml) Monovetten

Riessen, PloS One 2015;10:e0138879

outcome?

- mean **blood loss** per ICU day decreased from **43.3 ml** to **15.0 ml** *(P < 0.001)*
- observation days with recorded **Hb < 9 g/dl** decreased from **21.2%** to**15.4%** *(P = 0.01)*
- **transfused EBR** decreased from **7** to **2.3** *(P < 0.001)*
- **ICU LOS** decreased from **13.0** to **9.9** *(P = 0.014)*
- mean number of **ventilation days** was **7.1** days vs **7.5** days *(P = NS)*

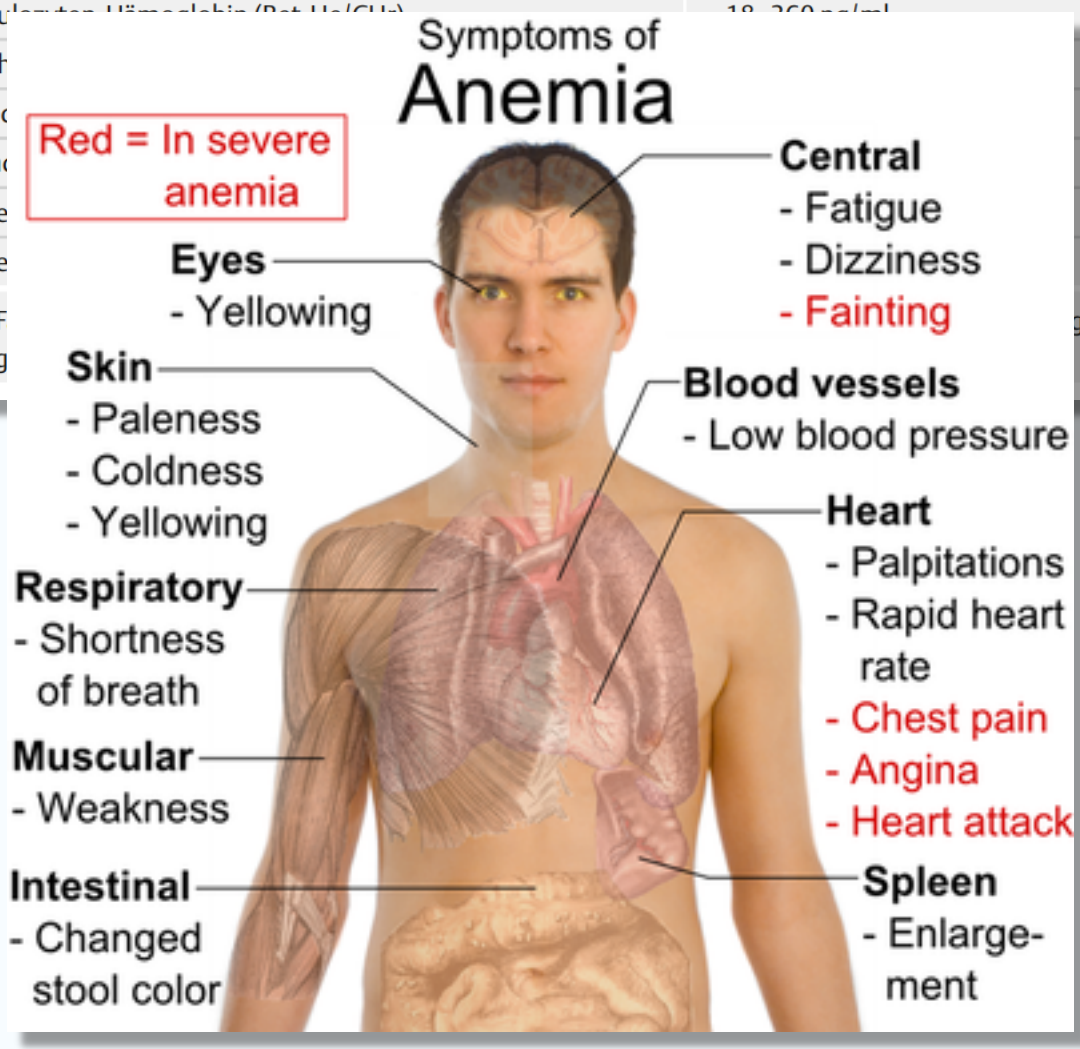
Riessen, PloS One 2015;10:e0138879

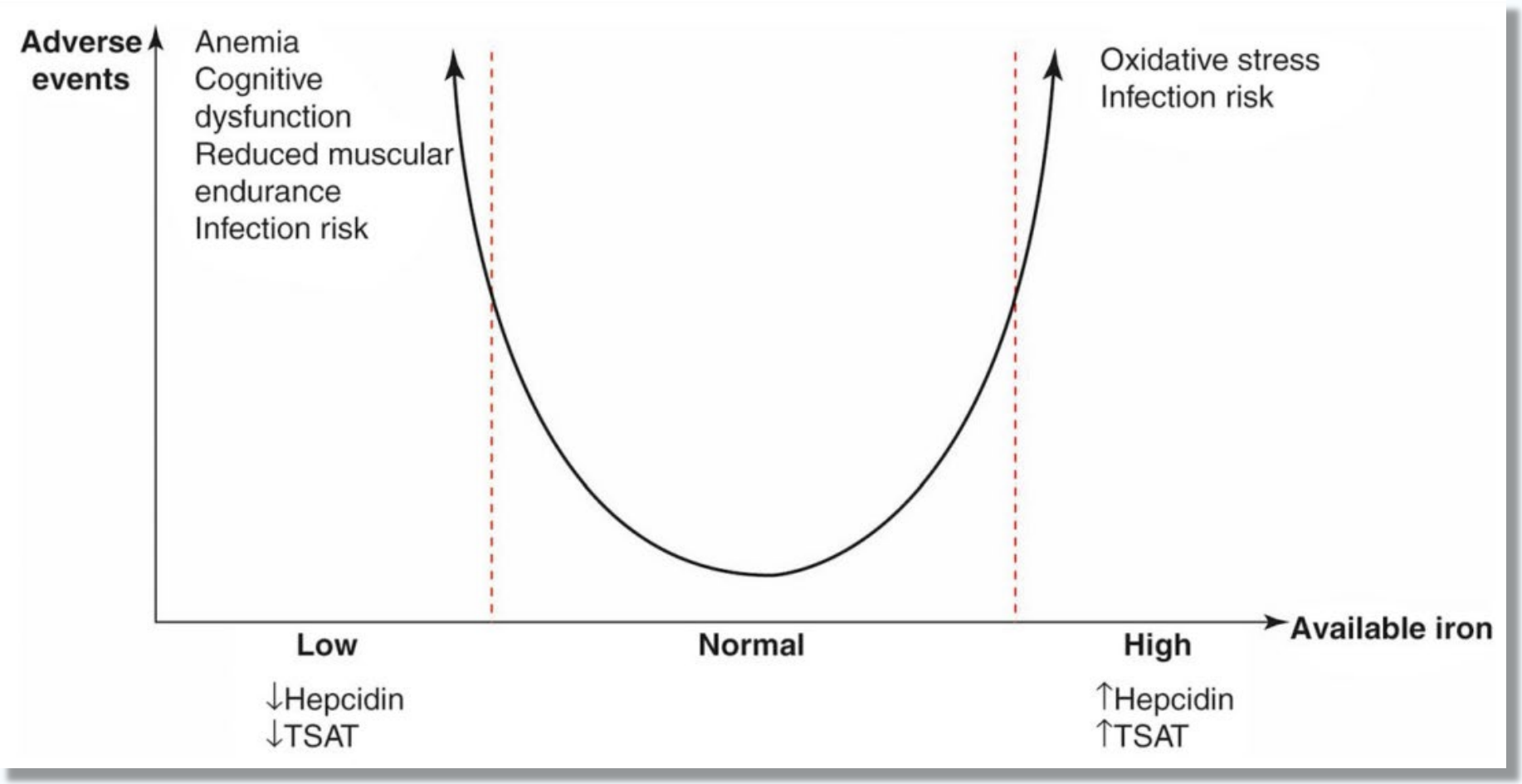
nedostatek železa

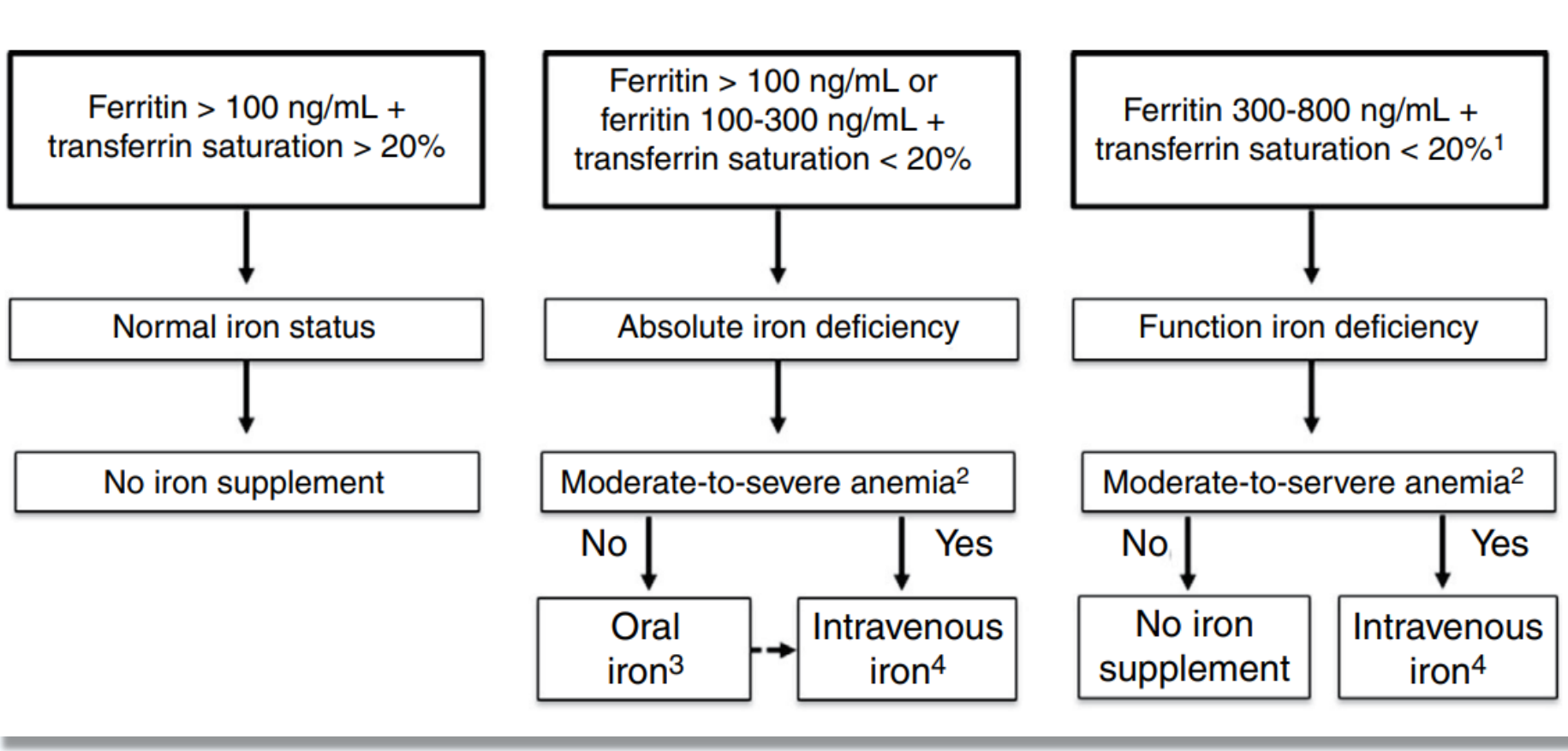
▶ **Tab. 2** Laborparameter und ihre Normwerte und Abweichungen bei Eisenmangelanämie.

Parameter	normal	Eisenmangelanämie
Transferrin-Sättigung	16–45 %	< 20 %
Ferritin	18–360 ng/ml	< 100 ng/ml*
Retiku	18–360 ng/ml	< 30 ng/ml
löslich		
▪ Roc		> 1,7 mg/l
▪ Dac		> 5 mg/l
mittle		< 27 pg
mittle		< 80 fl

* Im F … gelanämie bereits ab Ferritin-Werten von < 300 ng/l diag …




Adverse events
Anemia
Cognitive dysfunction
Reduced muscular endurance
Infection risk
Oxidative stress
Infection risk
Low
Normal
High
Available iron
↓Hepcidin
↓TSAT
↑Hepcidin
↑TSAT


Ferritin > 100 ng/mL + transferrin saturation > 20%
Normal iron status
No iron supplement
Ferritin > 100 ng/mL or ferritin 100-300 ng/mL + transferrin saturation < 20%
Absolute iron deficiency
Moderate-to-severe anemia2
No
Yes
Oral iron3
Intravenous iron4
Ferritin 300-800 ng/mL + transferrin saturation < 20%1
Function iron deficiency
Moderate-to-servere anemia2
No
Yes
No iron supplement
Intravenous iron4

iron

vs

infection?

iron

- is required for **host immunity** and **pathogen replication**
- in health is tightly **regulated** by the **hepcidin**
- **inflammation** triggers a process of withholding **free iron** from invading pathogens ***(nutritional immunity)***

Shah, JAMA Network Open. 2021;4:11.

iron

- i.v. iron **increases** the levels of circulating non–transferrin-bound **iron**
- increased levels of non–transferrin-bound iron are associated with **impaired T-cell** and **neutrophil** function
- it may be **promoting** pathogen **growth**

- *conversely, preexisting iron deficiency or restriction can impair T-cell, B-cell, and neutralizing antibody responses to infection*

Shah, JAMA Network Open. 2021;4:11.

benefit vs risk

- i.v. iron **decreases** the severity of **anaemia**
- **improves** clinical **outcomes** in non– critically ill patients
- iron therapy was **safe** and improves **haemoglobin** in critically ill patients (and maybe improves outcome?)

- is there an **association** between intravenous iron and **infection**?
- if so, does this association increase **morbidity** and **mortality**?

Shah, JAMA Network Open. 2021;4:11.

JAMA Network Open. 2021;4:11.

JAMA Network | Open™

Original Investigation | Hematology

Risk of Infection Associated With Administration of Intravenous Iron
A Systematic Review and Meta-analysis

Akshay A. Shah, MSc; Killian Donovan, BM, BCh; Claire Seeley, MBBS; Edward A. Dickson, BMBS; Antony J. R. Palmer, DPhil; Carolyn Doree, PhD; Susan Brunskill, MSc; Jack Reid, MBBS; Austin G. Acheson, MD; Anita Sugavanam, MBBS; Edward Litton, PhD; Simon J. Stanworth, DPhil

Abstract

IMPORTANCE Intravenous iron is recommended by many clinical guidelines based largely on its effectiveness in reducing anemia. However, the association with important safety outcomes, such as infection, remains uncertain.

OBJECTIVE To examine the risk of infection associated with intravenous iron compared with oral iron or no iron.

DATA SOURCES Medline, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for randomized clinical trials (RCTs) from 1966 to January 31, 2021. Ongoing trials were sought from ClinicalTrials.gov, CENTRAL, and the World Health Organization International Clinical Trials Search Registry Platform.

STUDY SELECTION Pairs of reviewers identified RCTs that compared intravenous iron with oral iron or no iron across all patient populations, excluding healthy volunteers. Nonrandomized studies published since January 1, 2007, were also included. A total of 312 full-text articles were assessed for eligibility.

DATA EXTRACTION AND SYNTHESIS Data extraction and risk of bias assessments were performed according to the Preferred Reporting Items of Systematic Reviews and Meta-analyses (PRISMA) and

Key Points

Question In patients who require treatment with intravenous iron, what is the evidence that this intervention increases the risk of developing a new infection?

Findings In this systematic review and meta-analysis of 154 randomized clinical trials that included 32 762 participants, intravenous iron was associated with an increased risk of infection.

Meaning The results of this study suggest that, despite broad advocacy in clinical guidelines, intravenous iron may increase the risk of infection, which must be balanced with the potential benefits of treating anemia and reducing blood transfusion requirements.

JAMA Network Open. 2021;4:11.

JAMA Network Open

Original Investigation | Hematology

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A Systematic Review and Meta-analysis

Akshay A. Shah, MSc; Killian Donovan, BM, BCh; Claire Seeley, MBBS; Edward A. Dickson, BMBS; Antony J. R. Palmer, DPhil; Carolyn Doree, PhD; Susan Brunskill, MSc; Jack Reid, M

MAIN OUTCOMES AND MEASURES The primary outcome was risk of infection. Secondary outcomes included mortality, hospital length of stay, and changes in hemoglobin and red blood cell transfusion requirements. Measures of association were reported as risk ratios (RRs) or mean differences.

RESULTS A total of 154 RCTs (32 762 participants) were included in the main analysis. Intravenous iron was associated with an increased risk of infection when compared with oral iron or no iron (RR, 1.16; 95% CI, 1.03-1.29; I^2 = 36%; moderate certainty of evidence). Intravenous iron also was associated with an increase in hemoglobin (mean difference, 0.57 g/dL; 95% CI, 0.50-0.64 g/dL; I^2 = 94%) and a reduction in the risk of requiring a red blood cell transfusion (RR, 0.93; 95% CI, 0.76-0.89; I^2 = 15%) when compared with oral iron or no iron. There was no evidence of an effect on mortality or hospital length of stay.

CONCLUSIONS AND RELEVANCE In this large systematic review and meta-analysis, intravenous iron was associated with an increased risk of infection. Well-designed studies, using standardized definitions of infection, are required to understand the balance between this risk and the potential benefits.

prevence:

- review and meta-analysis of **154 RCTs** (32.762 pts)
- **i.v. iron** was associated with an increased **risk of infection** (moderate certainty of evidence)
- there was substantial variation and **inconsistency** in how **infection** was defined and reported
- i.v. iron remained associated with **improved Hb** levels and **reduced RBC transfusion** requirements
- we observed **no differences** in **mortality** or **hospital length of stay**

JAMA Network Open. 2021;4:11.

Table 2. Association Between Intravenous Iron and Primary and Secondary Outcomes

Outcome	No. of studies	No. of participants[a]		Treatment effect	*P* value	I^2, %
		Intravenous iron	Oral iron or no iron			
Primary outcome						
Infection	64	1101/10 010	955/9312	RR (95% CI): 1.16 (1.03 to 1.29)	.003	36
Continuous outcomes						
Hemoglobin	110	10 816	9720	MD (95% CI): 0.57 (0.50 to 0.64) g/dL	<.001	94
RBCs transfused	11	998	956	MD (95% CI): −0.20 (−0.32 to −0.08) cells	<.001	81
Hospital LOS	8	807	883	MD (95% CI): −0.43 (−1.10 to 0.24) d	.05	50
Dichotomous outcomes						
Treatment response[b]	60	4336/7137	2611/6165	RR (95% CI): 1.46 (1.32 to 1.60)	<.001	92
Mortality						
Short term (≤30 d)	15	40/1298	40/1292	RR (95% CI): 0.99 (0.69 to 1.42)	.73	0
Long term (>30 d)	12	165/2752	161/2258	RR (95% CI): 0.94 (0.75 to 1.18)	.63	0
Requirement for RBC transfusion	54	802/6256	989/6040	0.83 (0.76 to 0.89)	<.001	15

Contents lists available at ScienceDirect

Transfusion Medicine Reviews

journal homepage: https://www.journals.elsevier.com/transfusion-medicine-reviews

Available online 24 December 2021

Efficacy and Safety of Intravenous Iron Therapy for Treating Anaemia in Critically ill Adults: A Rapid Systematic Review With Meta-Analysis

Louise J Geneen[a,b,*], Catherine Kimber[a,b], Carolyn Doree[a,b], Simon Stanworth[a,b,c], Akshay Shah[b,c]

[a] *Systematic Review Initiative, NHS Blood and Transplant, Oxford, UK*
[b] *Nuffield Division of Clinical Laboratory Sciences, Radcliffe Department of Medicine, University of Oxford, Oxford, UK*
[c] *Oxford University Hospitals NHS Foundation Trust, Oxford, UK*

Rapid Systematic Review With Meta-Analysis:

- the **efficacy** and **safety** of **i.v. iron** therapy for treating anaemia in **critically ill** adults admitted to ICU
- **1198** pts in **8** RCTs

main findings from this review:

- **i.v. iron** continues to demonstrate **improving of Hb** at intermediate follow up of 10 to 30 days
- **i.v. iron** appears **to be safe** with **no evidence** of an effect on **infection** or **mortality**

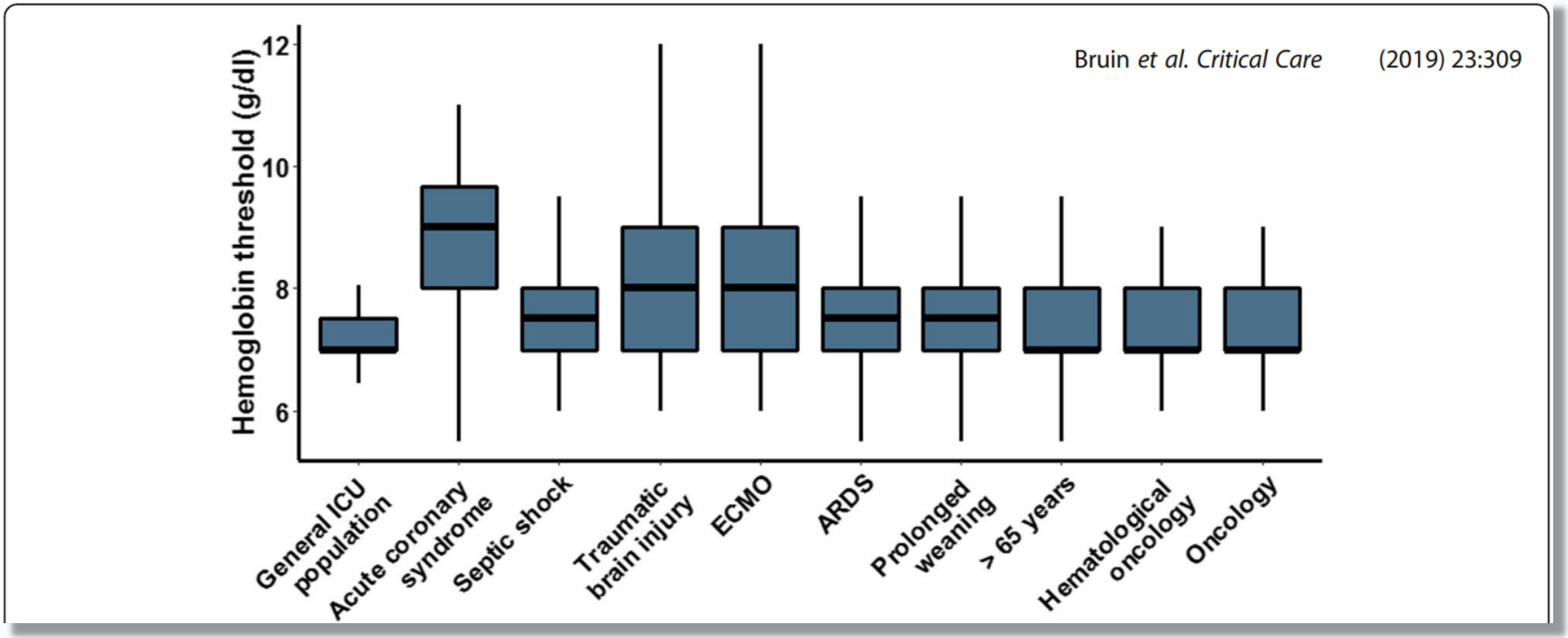
tolerance

anémie

RESEARCH Open Access

Transfusion practice in the non-bleeding critically ill: an international online survey—the TRACE survey

Sanne de Bruin[1,2], Thomas W. L. Scheeren[3], Jan Bakker[4,5,6], Robin van Bruggen[2], Alexander P. J. Vlaar[1*] and on behalf of the Cardiovascular Dynamics Section and Transfusion Guideline Task Force of the ESICM



the use of iron in ICU

- to improve erythropoiesis and prevent RCC transfusion:

  - **41%** of respondents use iron as a monotherapy
  - **17%** of respondents use iron in combination with erythropoietin
  - **12%** of respondents use erythropoietin as a monotherapy

de Bruin, Critical Care. 2019;23:309.

The use of transfusion triggers in addition to a Hb threshold

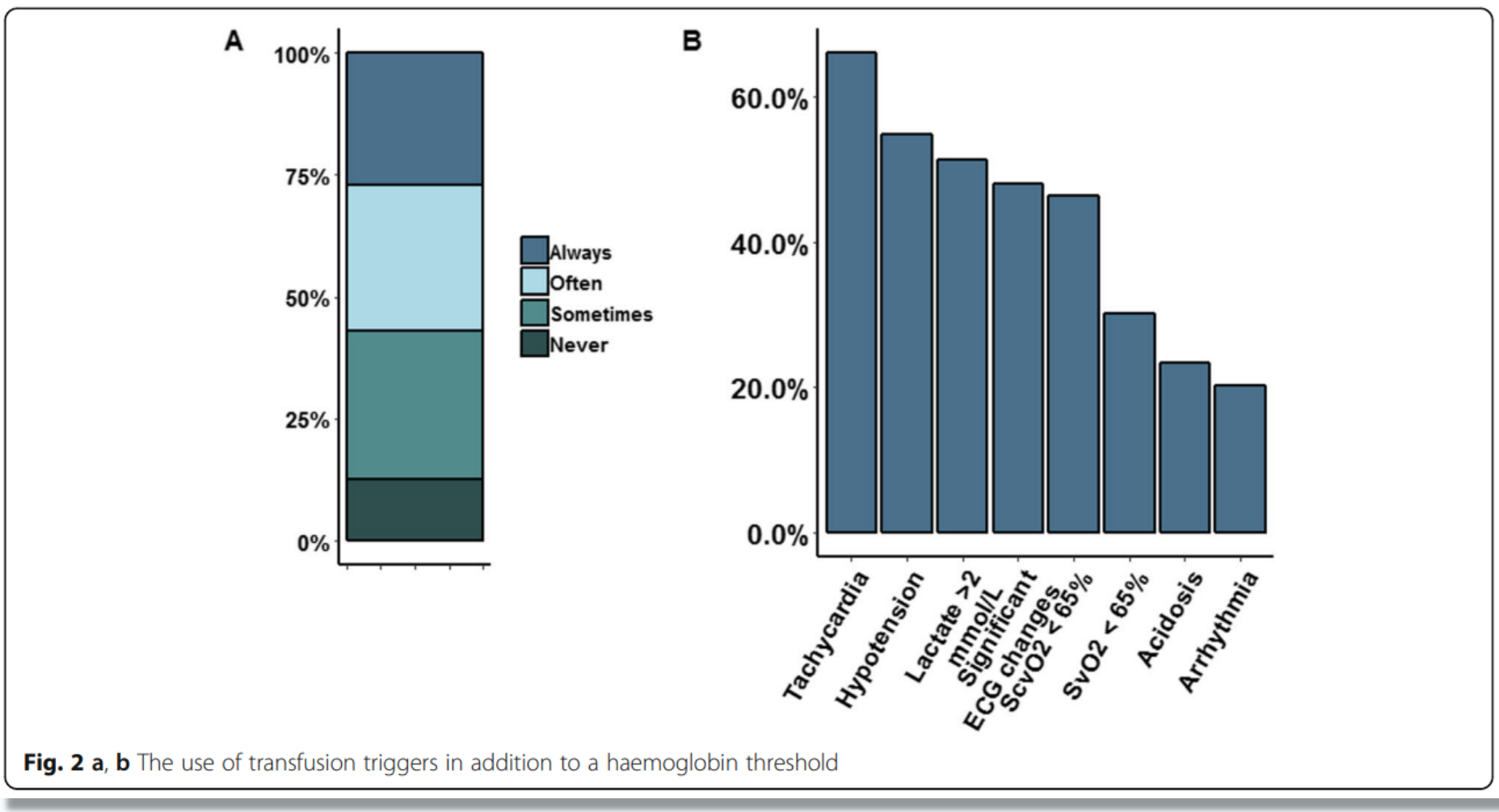


Fig. 2 a, **b** The use of transfusion triggers in addition to a haemoglobin threshold

hepcidin

hepcidin

- peptid (25 aminokyselin), charakter **hormonu**
- izolován v r. 2000 z lidské moči
- syntéza v játrech ***(hep-)*** + antibakt. vlastnosti ***(-cidin)***
- snižuje **absorpci** železa v enterocytech
- snižuje **export** železa z enterocytů a makrofágů
- **snížení erytropoezy** (vzniká anémie)
- ukrytí **železa** před bakteriemi
- stanovení hladiny jako alternativa **feritinu**?

Park, J. Biol. Chem. 2001;276(11):7806-10

Lasocki *et al. Crit Care* (2021) 25:62
https://doi.org/10.1186/s13054-020-03430-3

Critical Care

RESEARCH Open Access

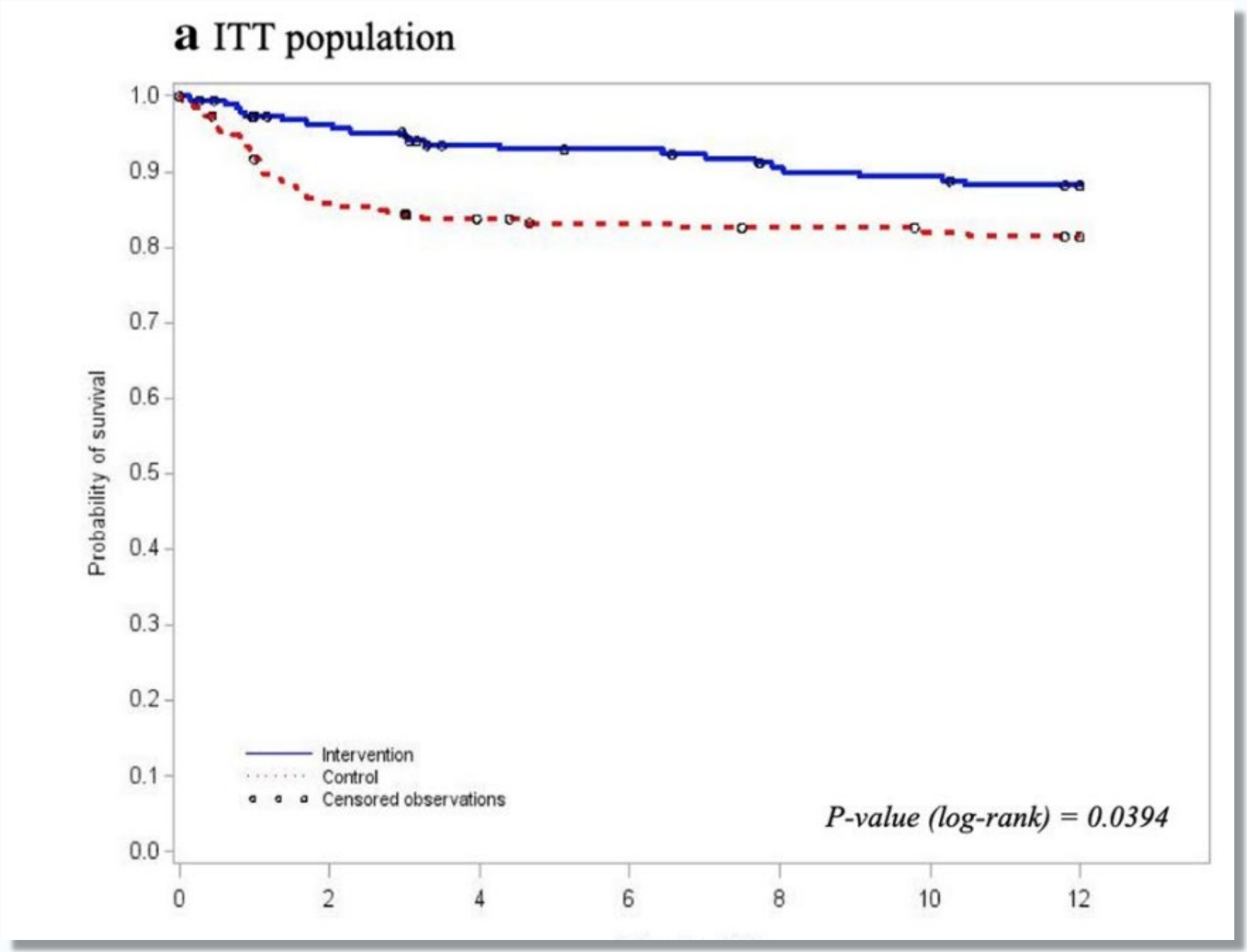
Impact of treating iron deficiency, diagnosed according to hepcidin quantification, on outcomes after a prolonged ICU stay compared to standard care: a multicenter, randomized, single-blinded trial

Results: Of 405 randomized patients, 399 were analyzed (201 in intervention and 198 in control arm). A total of 220 patients (55%) had ID at discharge (i.e., a hepcidin < 41 µg/l). Primary endpoint was not different (medians (IQR) post-ICU LOS 33(13;90) vs. 33(11;90) days for intervention and control, respectively, median difference − 1(− 3;1) days, $p = 0.78$). D90 mortality was significantly lower in intervention arm (16(8%) vs 33(16.6%) deaths, absolute risk difference − 8.7 (− 15.1 to − 2.3)%, $p = 0.008$, OR 95% IC, 0.46, 0.22–0.94, $p = 0.035$), and one-year survival was improved ($p = 0.04$).

Conclusion: Treatment of ID diagnosed according to hepcidin levels did not reduce the post-ICU LOS, but was associated with a significant reduction in D90 mortality and with improved 1-year survival in critically ill patients about to be discharged after a prolonged stay.

RCT N = 399 France Multi-centre (8)	critically ill (any critical illness) Age: mean 63 y	Hepcidin quantification and treatment as required: Iron if hepcidin </=20mcg/L Iron+EPO if hepcidin </= 41mcg/L [Iron: 1g ferric carboxymaltose (single dose); EPO: epoetin alpha (Eprex, Janssen, France) 40.000 UI subcutaneously (single dose, EPO injection repeated weekly if pt still anaemic]

• Hb at 15 ds post-ICU discharge • Hospital LOS (post-ICU) • 90-d mortality • HRQoL: fatigue, MFI-20


a ITT population
Probability of survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
2
4
6
8
10
12
Intervention
Control
Censored observations
P-value (log-rank) = 0.0394

jak

substituovat?

jaké železo?

- ferric carboxymaltose
- ferumoxytol
- iron sucrose
- ferric derisomaltose
- sodium ferric gluconate
- iron dextran

Frigstad, Gastroenterol Res Pract. 2017;4585164.

LaVallee, Journal of Blood Medicine. 2022;13:133-42.

Journal of Blood Medicine

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Relationship Between Initial Parenteral Iron Therapy Dosing and Treatment Effectiveness: A Real-World Retrospective Analysis

Chris LaVallee[1], Isha Bansal[2], Shilpa Kamdar[2], Winghan Jacqueline Kwong[3], Ralph V Boccia[4]

[1]Health Outcomes Research, Decision Resources Group, Burlington, MA, USA; [2]Analytics, Decision Resources Group, Burlington, MA, USA; [3]Health Economics & Outcomes Research, Daiichi Sankyo Inc., Basking Ridge, NJ, USA; [4]Center for Cancer and Blood Disorders, P.C, Bethesda, MD, USA

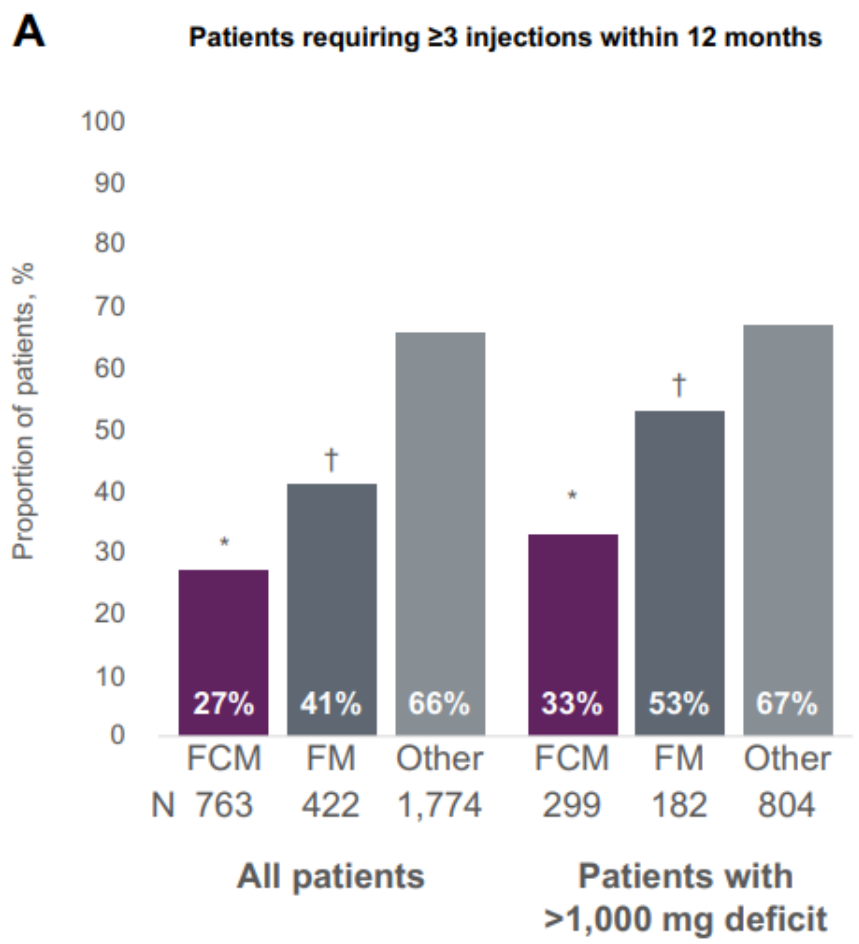
Correspondence: Winghan Jacqueline Kwong, Daiichi Sankyo, Inc., 211 Mt Airy Road, Basking Ridge, NJ, 07920, USA, Tel +1 908 992 7063, Email jkwong@dsi.com

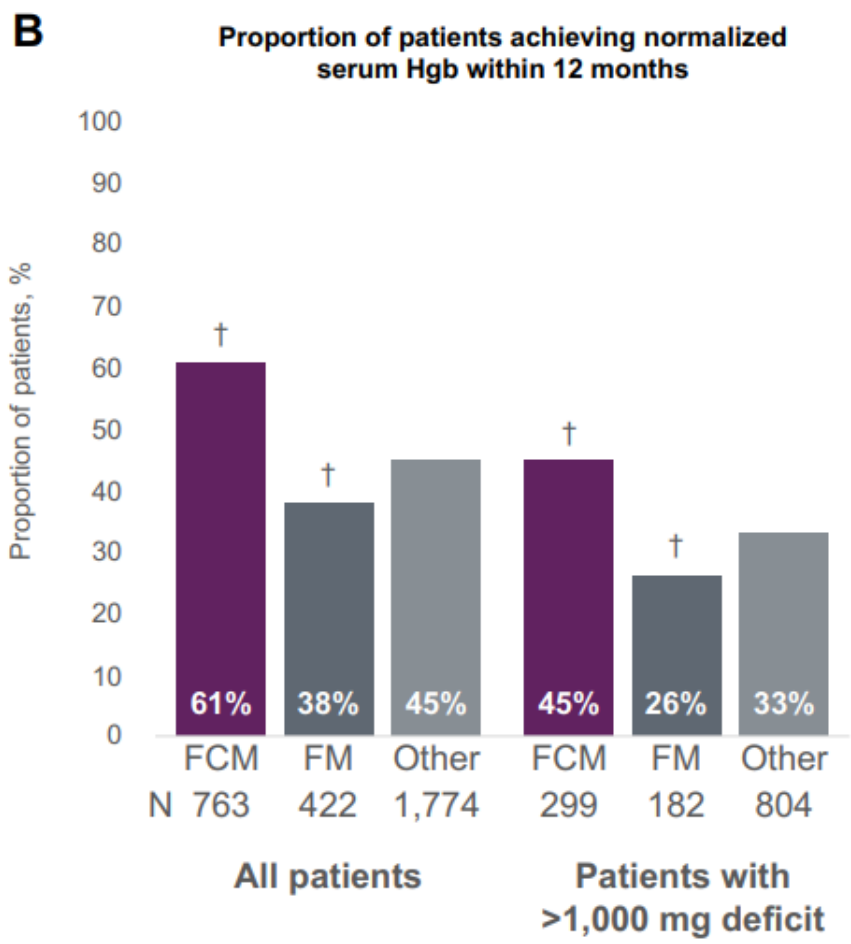
Purpose: Replacement iron is the main treatment for iron deficiency, but the relationship between initial intravenous (IV) dose and need for additional treatment is unclear. This study explored patterns of IV iron dosing in US clinical practice.

Methods: Patient records were obtained for adults who received IV iron for anemia between 2015 and 2017. Patients were classified into four groups: those who received <1500 mg and ≥1500 mg IV iron and those received ≤1000 mg and >1000 mg within 3 weeks of their first dose. The proportion of patients requiring additional IV iron after 30 days of the initial dose was evaluated.

Results: Data were obtained for 2959 patients receiving iron sucrose (44.2%), ferric carboxymaltose injection (FCM) (25.8%), and

Parenteral iron therapies that are currently available in the US vary in dose and administration schedule, and include ferric carboxymaltose (FCM), ferumoxytol (FM), iron sucrose, ferric derisomaltose, sodium ferric gluconate, and iron dextran.[11]



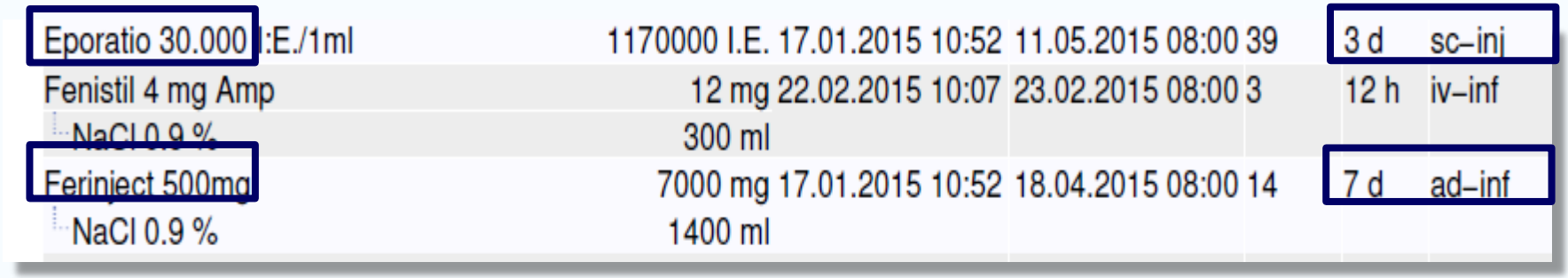


Notes: *Statistically significant difference vs FM ($p < 0.001$); †statistically significant difference vs other ($p < 0.001$).
Abbreviations: FCM, ferric carboxymaltose; FM, ferumoxytol; Hgb, hemoglobin; IV, intravenous.

Landesklinikum Baden bei Wien

terapie železem

- po zvládnutí nebo nepřítomnosti **floridní infekce**
- u **anémie** při poklesu Hb cca pod **10 g/dl**
- **Ferinject** 1000 mg i.v. á 7 dní (celkem 2 dávky)
- **EPO** 30.000 IU s.c. á 3 dny
- zvl. u odmítajících transfúzi, CNI,
  vzácná krevní skupina, protilátky …
-



Eporatio 30.000 I:E./1ml	1170000 I.E.	17.01.2015 10:52	11.05.2015 08:00	39	3 d	sc–inj
Fenistil 4 mg Amp	12 mg	22.02.2015 10:07	23.02.2015 08:00	3	12 h	iv–inf
NaCl 0.9 %	300 ml					
Ferinject 500mg	7000 mg	17.01.2015 10:52	18.04.2015 08:00	14	7 d	ad–inf
NaCl 0.9 %	1400 ml					

Eporatio 30.000 IU s.c. á 3d (17.1. – 11.5.2017)

celkem **1.170.000 IU**

Ferinject 500 mg i.v. á 7d (17.1. – 18.4.2017)

celkem **7.000 mg**

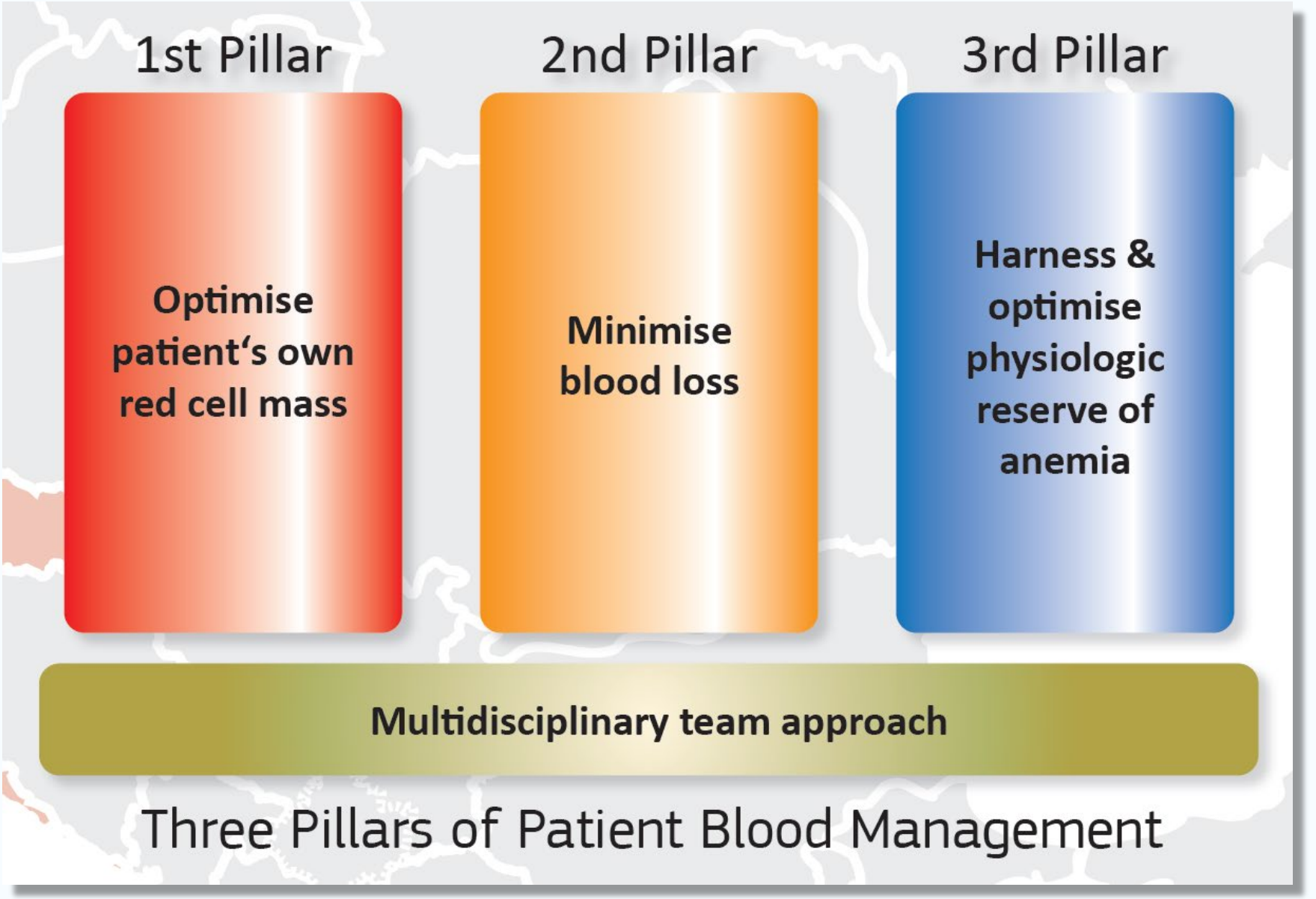

with permission


with permission

summary

- the potential **impact** of iron therapy for treating anaemia in survivors of critical illness remains **unclear**
- **i.v. iron** continues to **improve Hb** **without** any clear signal of **harm**
- recent trials have **suggested** that there may be an **improvement** in long-term morbidity
- **ferric carboxymaltose** should be **prefered**
- iron should **not be given** in acute severe **infection**
- iron therapy should be a part of **PBM**

Geneen. Transfusion Medicine Reviews.: 2022;18:37.


1st Pillar
2nd Pillar
3rd Pillar
Optimise patient's own red cell mass
Minimise blood loss
Harness & optimise physiologic reserve of anemia
Multidisciplinary team approach
Three Pillars of Patient Blood Management


...děkuji Vám za pozornost