



Sanquin



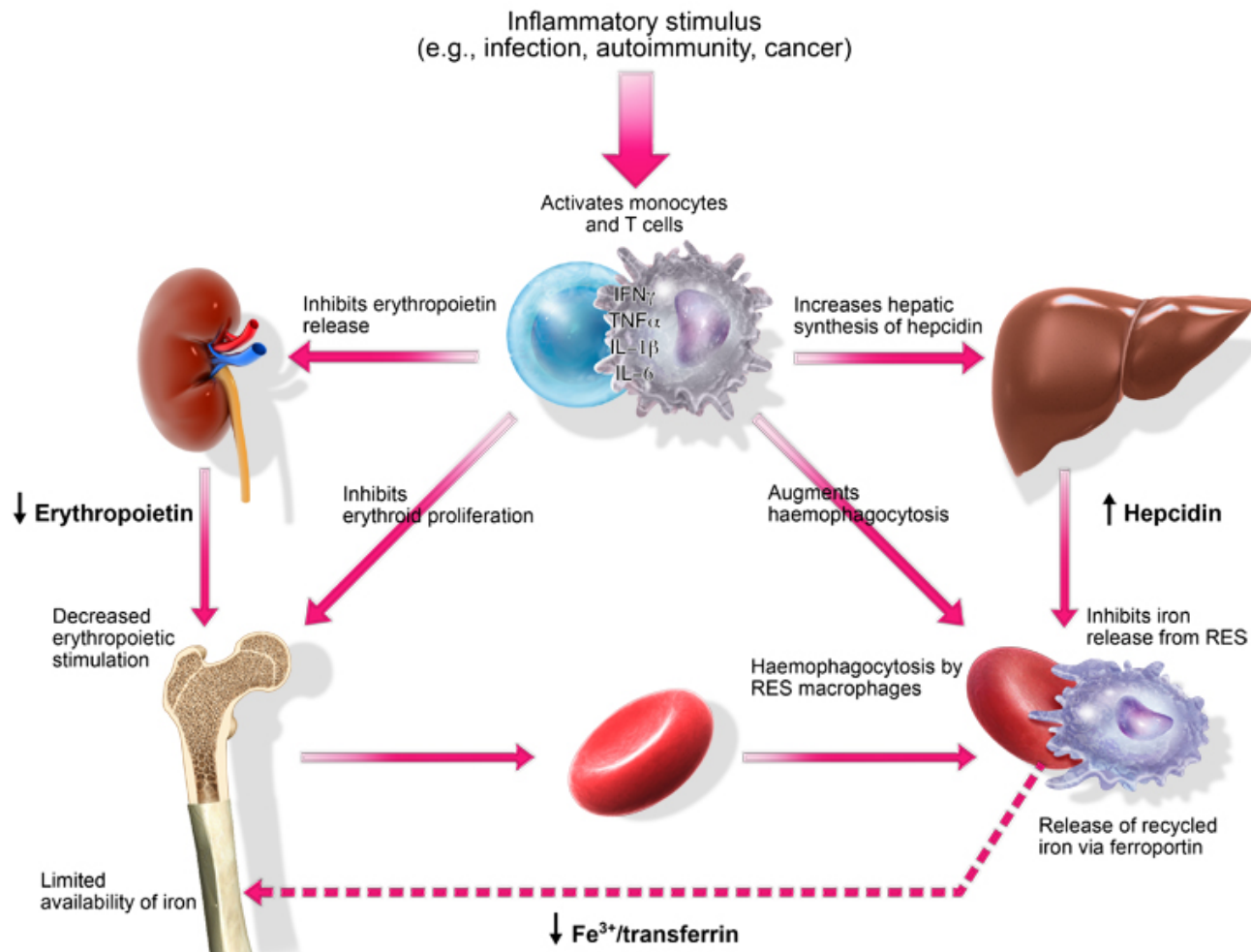
IJzermetabolisme in IC patiënten

Robin van Bruggen

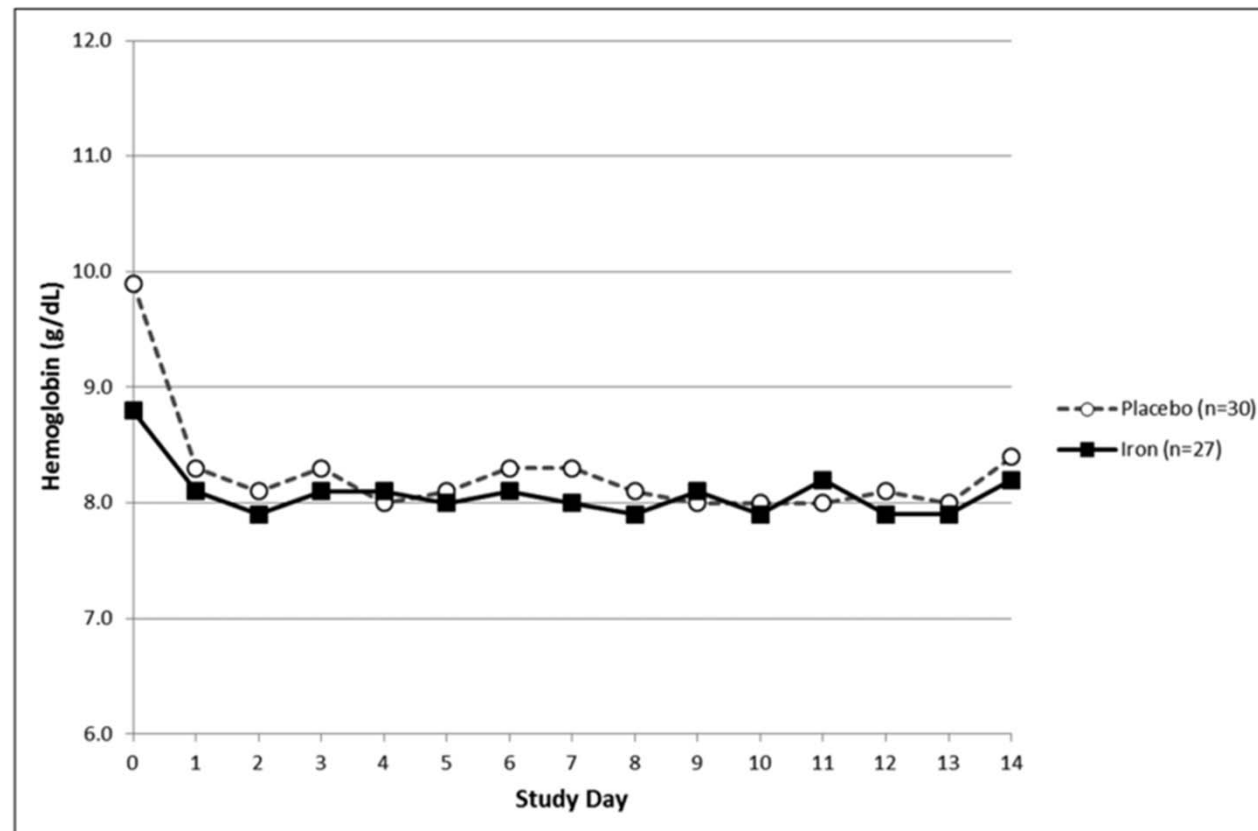
BloedCel Research



Anemia of inflammation



A multicenter, randomized clinical trial of IV iron supplementation for anemia of traumatic critical illness



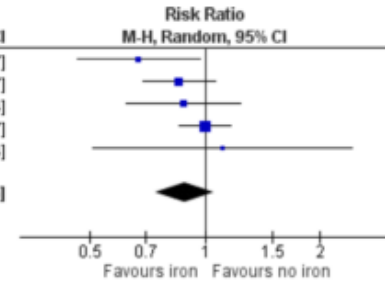
Pieracci et al., *Critical Care Medicine* 2014



Meta-analysis Iron vs. Placebo in critically ill

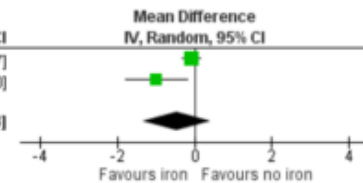
(a) Requirement for RBC transfusion

Study or Subgroup	Iron		No iron		Weight	M-H, Random, 95% CI
	Events	Total	Events	Total		
Pieracci 2009	29	97	46	103	15.5%	0.67 [0.46, 0.97]
Pieracci 2014	47	75	55	75	27.5%	0.85 [0.68, 1.07]
Garrido-Martin 2012	47	107	26	52	17.1%	0.88 [0.62, 1.24]
van Iperen 2000	12	12	12	35.3%	1.00 [0.86, 1.17]	1.00 [0.86, 1.17]
Madi-Jebara 2004	10	40	9	40	4.6%	1.11 [0.51, 2.44]
Total (95% CI)		331		282	100.0%	0.88 [0.74, 1.06]
Total events	145		148			
Heterogeneity: Tau ² = 0.02; Chi ² = 7.37, df = 4 (P = 0.12); I ² = 46%						
Test for overall effect: Z = 1.35 (P = 0.18)						



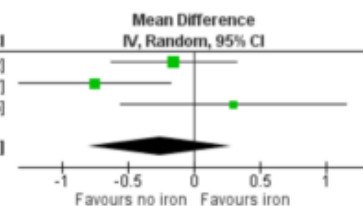
(b) Mean number of RBC units transfused

Study or Subgroup	Iron		No iron		Total	Weight	Mean Difference IV, Random, 95% CI	
	Mean	SD	Mean	SD				
Garrido-Martin 2012	-0.085	0.74	107	-0.01	0.73	52	58.8%	-0.08 [-0.32, 0.17]
van Iperen 2000	1.07	1.04	12	2.06	0.93	12	41.2%	-0.99 [-1.78, -0.20]
Total (95% CI)			119		64	100.0%	-0.45 [-1.34, 0.43]	
Heterogeneity: Tau ² = 0.33; Chi ² = 4.71, df = 1 (P = 0.03); I ² = 79%								
Test for overall effect: Z = 1.00 (P = 0.32)								



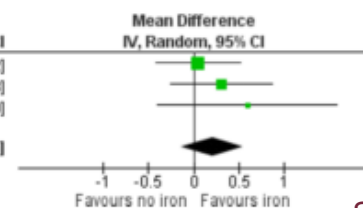
(c) Mean difference in Hb concentration (g/dL) (≤10 days)

Study or Subgroup	Iron		No iron		Total	Weight	Mean Difference IV, Random, 95% CI	
	Mean	SD	Mean	SD				
Garrido-Martin 2012	12.65	1.66	107	12.8	1.29	52	40.8%	-0.15 [-0.62, 0.32]
Madi-Jebara 2004	8.71	0.93	30	9.46	1.34	31	35.3%	-0.75 [-1.33, -0.17]
van Iperen 2000	10.3	1.1	10	10	0.9	12	23.9%	0.30 [-0.55, 1.15]
Total (95% CI)			147		95	100.0%	-0.25 [-0.79, 0.28]	
Heterogeneity: Tau ² = 0.13; Chi ² = 4.62, df = 2 (P = 0.10); I ² = 57%								
Test for overall effect: Z = 0.93 (P = 0.35)								



(d) Mean difference in Hb concentration (g/dL) (>10 days follow-up)

Study or Subgroup	Iron		No iron		Total	Weight	Mean Difference IV, Random, 95% CI	
	Mean	SD	Mean	SD				
Garrido-Martin 2012	11.05	1.4	107	11	1.44	52	52.0%	0.05 [-0.42, 0.52]
Madi-Jebara 2004	12.18	1.04	30	11.87	1.21	31	36.3%	0.31 [-0.26, 0.88]
van Iperen 2000	11.4	1.3	9	10.8	0.8	9	11.7%	0.60 [-0.40, 1.60]
Total (95% CI)			146		92	100.0%	0.21 [-0.13, 0.55]	
Heterogeneity: Tau ² = 0.00; Chi ² = 1.15, df = 2 (P = 0.56); I ² = 0%								
Test for overall effect: Z = 1.20 (P = 0.23)								



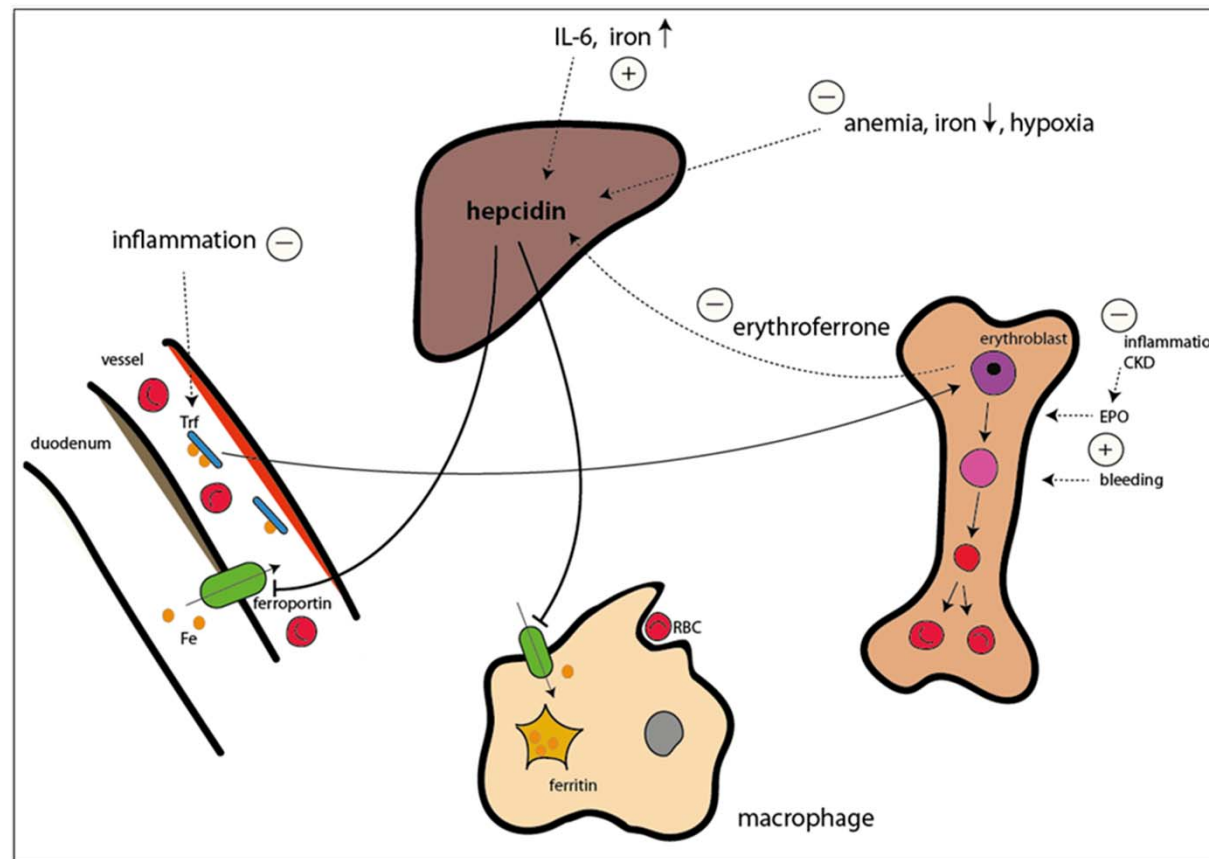
IRONMAN study, Litton et al. *ICM* 2016

- Inclusion: Hb < 10 g/dL
- Exclusion:
 - Ferritin > 1200 ng/ml or Tf saturation > 50 %
- Randomization: iron i.v. vs. placebo
- Result
 - Increased Hb at hospital discharge ($p=0.02$)
 - No difference RBC transfusions / mortality

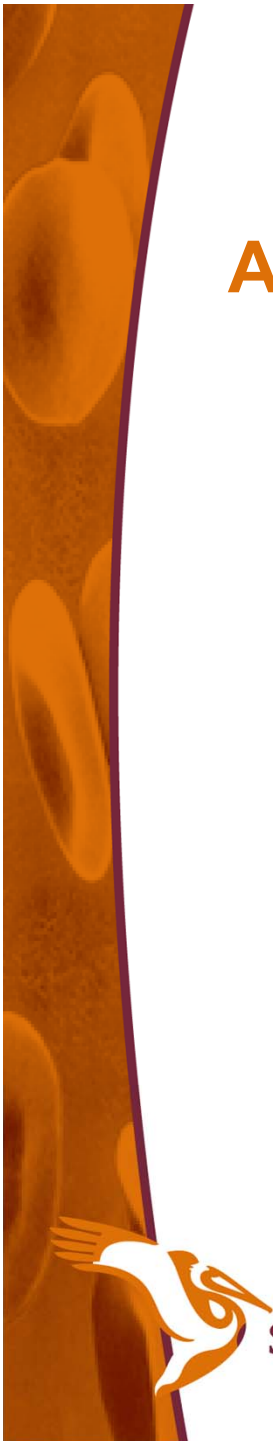


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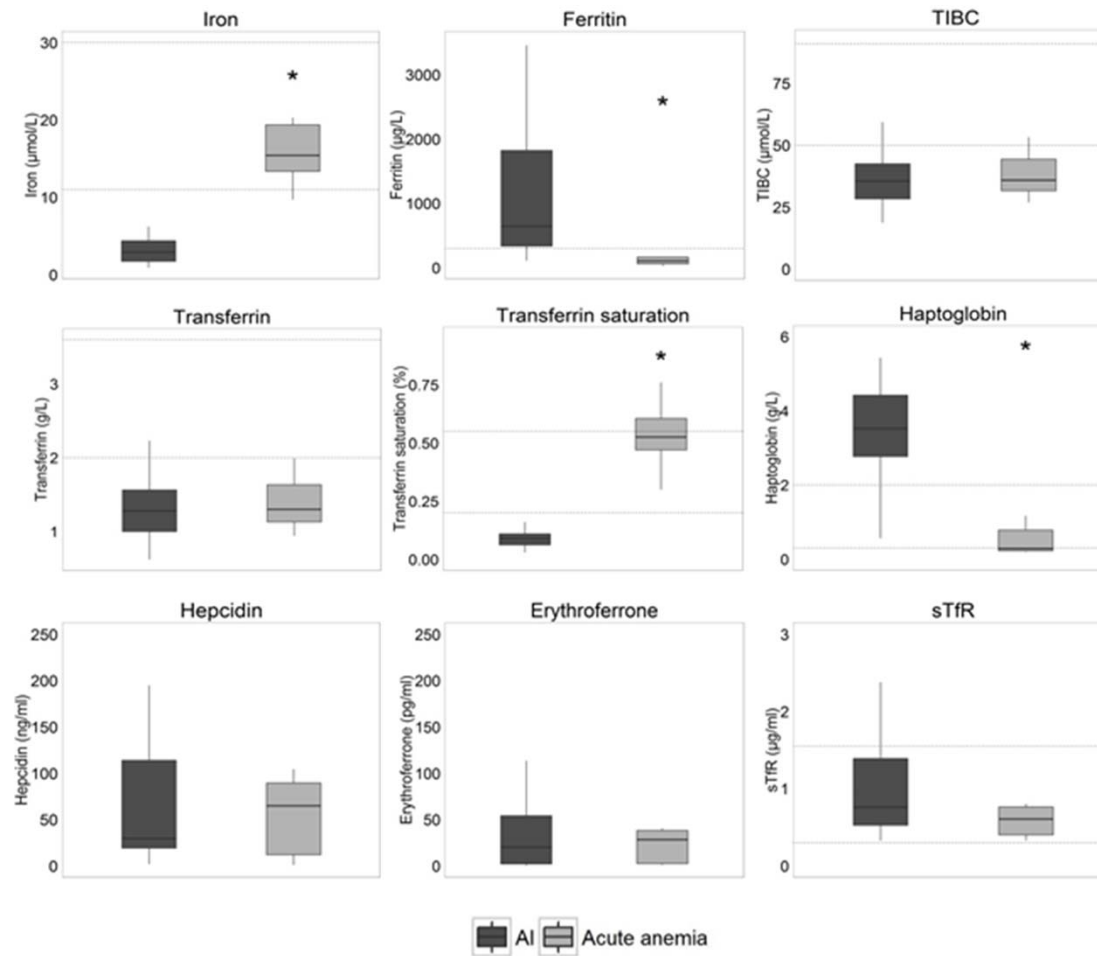
Anemia of inflammation



Iron metabolism in critically ill?
Therapy for AI?

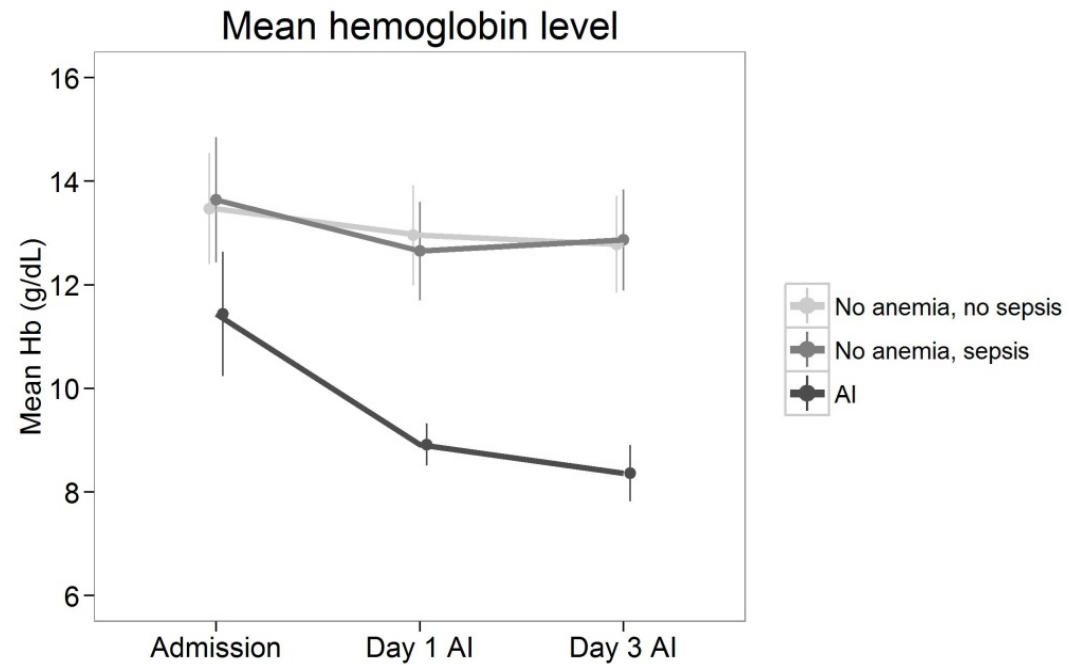


AI vs. Anemia due to acute blood loss

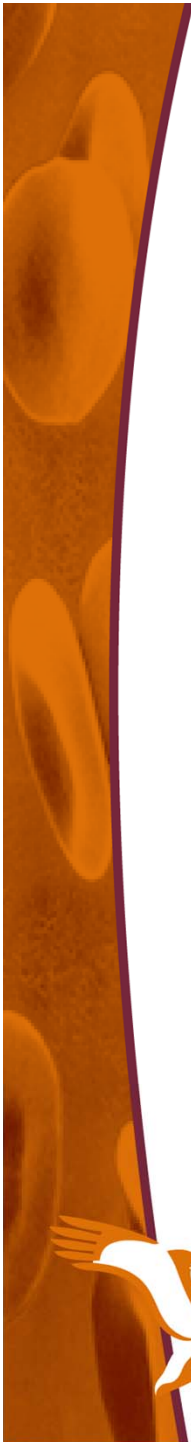
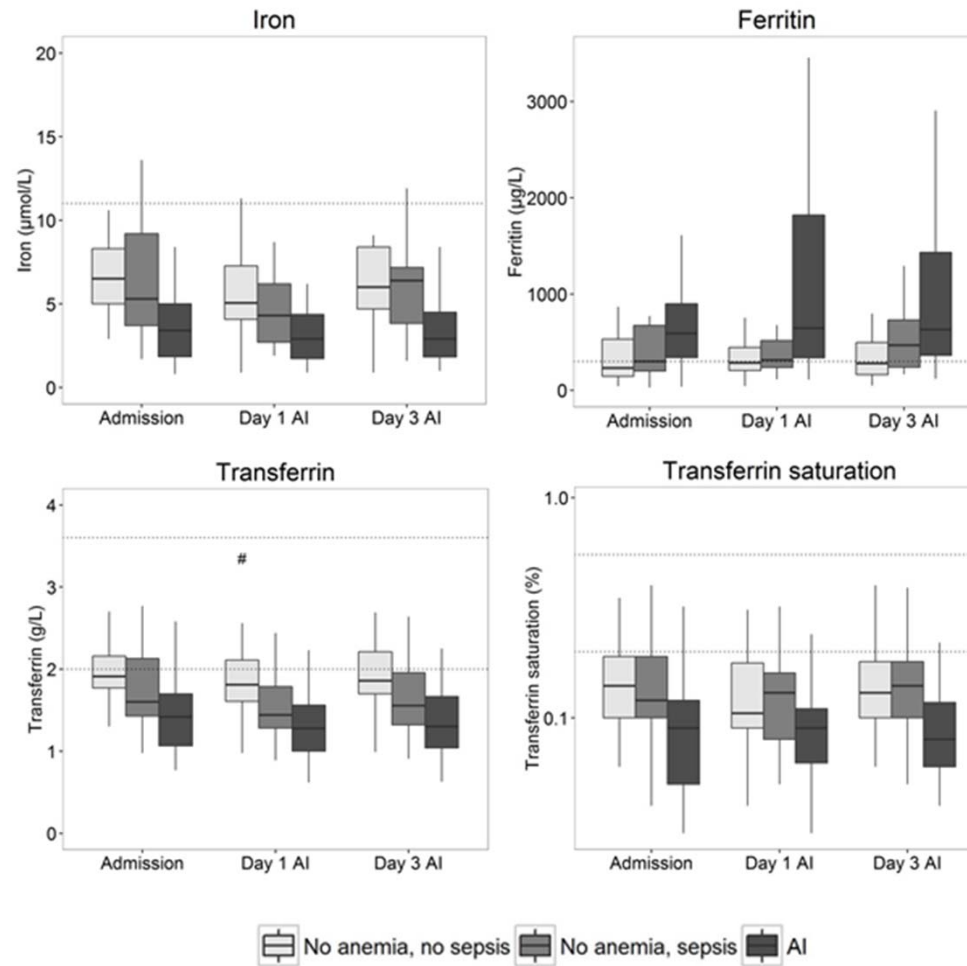


Iron metabolism in critically ill patients developing anemia of inflammation; a case control study

- 30 patients per group

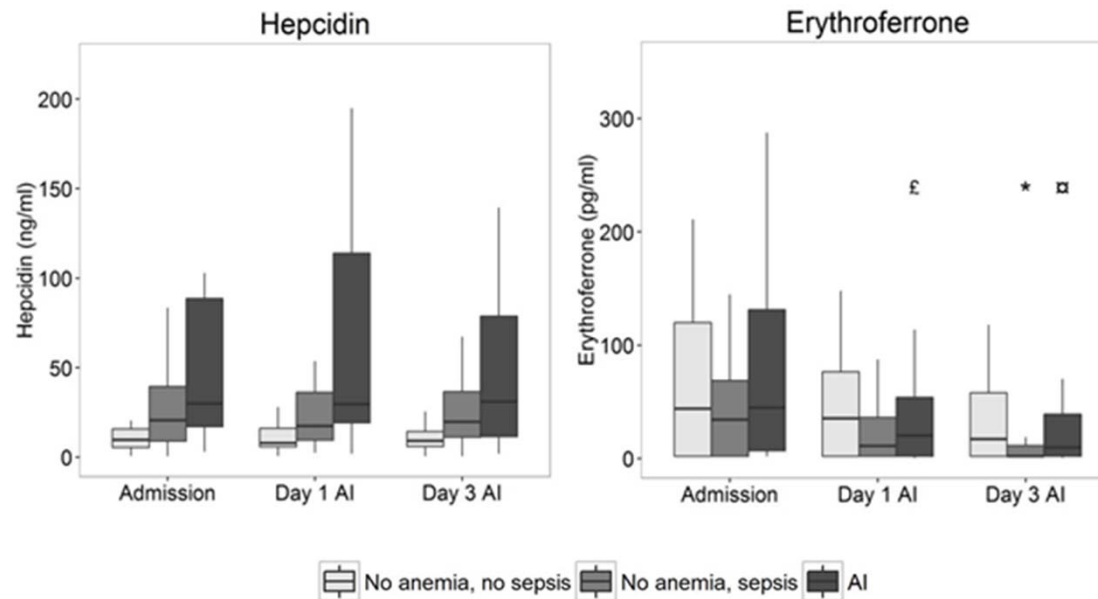


No differences during AI development



Hepcidin does not change over time

ERFE decreases during AI development



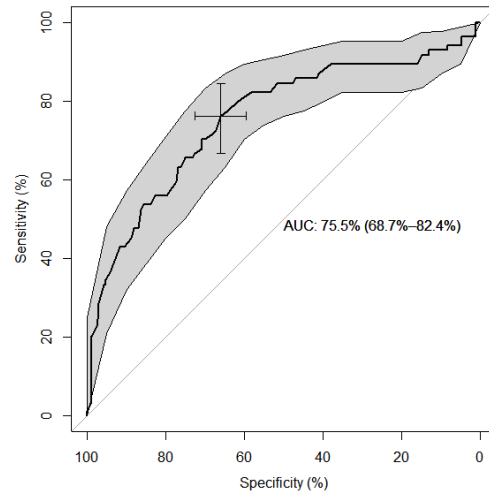
Most parameters show no difference over time!

Sanquin Iron metabolism altered in AI before anemia arises

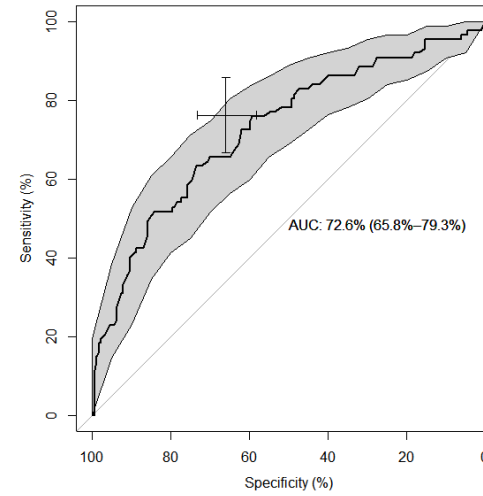


Use iron parameters to diagnose AI early?

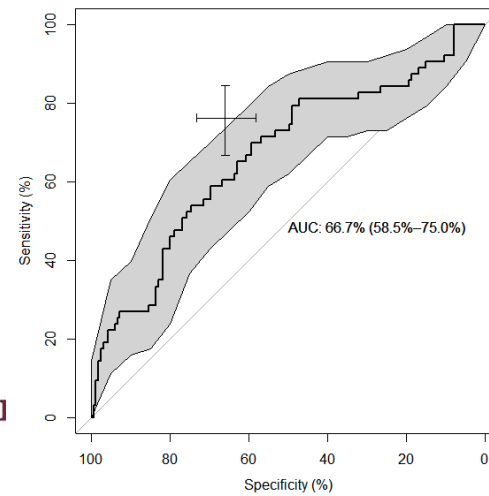
Iron



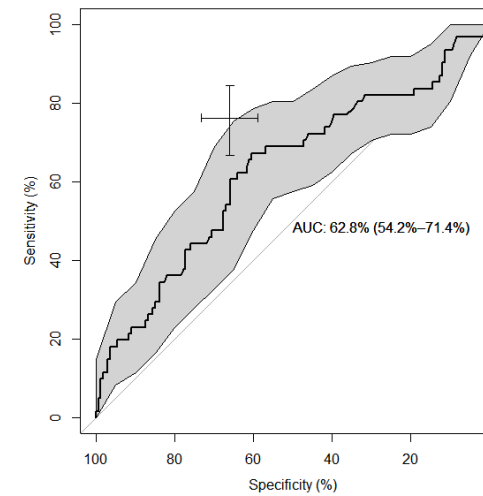
Transferrin



Hepcidin



Ferritin



Accuracy of diagnostic tests

Test characteristics and 95% CIs for iron parameters by the sensitivity, specificity

	Sensitivity	Specificity
Iron ¹	0.76 (0.66 to 0.85)	0.66 (0.61 to 0.71)
Transferrin	0.64 (0.53 to 0.74)	0.73 (0.69 to 0.78)
Hepcidin	0.73 (0.58 to 0.84)	0.58 (0.52 to 0.63)
Ferritin	0.69 (0.56 to 0.80)	0.57 (0.52 to 0.62)

Sensitivity: proportion of patients **with** AI correctly diagnosed

Specificity: proportion of patients **without** AI correctly diagnosed



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Positive and negative predictive values and 95% CIs for various prevalence values

	Pre-Test probability of disease (prevalence)		
	30%	53%^	70%
Iron			
PPV	49% (44 to 54)	72% (68 to 75)	84% (81 to 87)
NPV	87% (83 to 89)	71% (66 to 75)	54% (49 to 59)
Transferrin			
PPV	50% (45 to 56)	73% (68 to 77)	85% (81 to 88)
NPV	83% (79 to 85)	64% (60 to 68)	46% (42 to 51)
Hepcidin			
PPV	43% (38 to 47)	66% (62 to 70)	80% (77 to 83)
NPV	83% (80 to 87)	66% (61 to 70)	48% (43 to 53)
Ferritin			
PPV	41% (36 to 45)	64% (60 to 68)	79% (75 to 82)
NPV	81% (77 to 84)	62% (57 to 67)	44% (39 to 49)

^ Prevalence of anemia (Hb<7.5 for women and Hb<8.5 for men) in 2016 in a subset of a 30-bedded academic ICU department

PPV: proportion of positive test results that are true positive
 NPV: proportion of negative test results that are true negative



Conclusions

- Iron metabolism is altered in AI,
- Iron metabolism is altered in AI before anemia arises,
- Iron is a fair predictor of AI

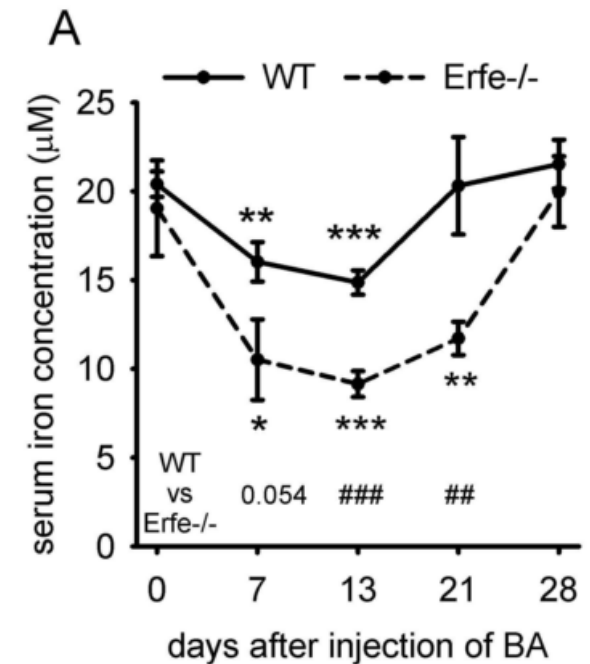
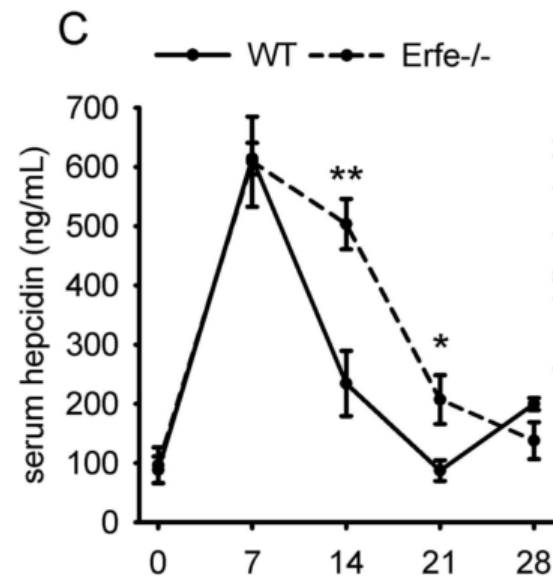
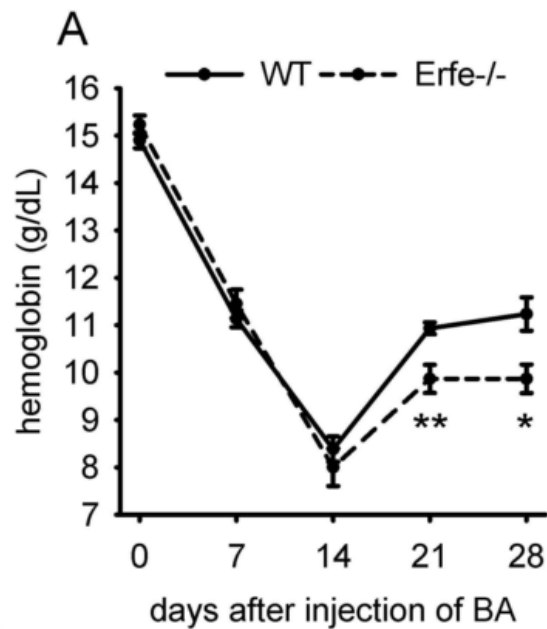
- Iron i.v. does not correct Hb level in ICU patients

- Iron + transferrin?



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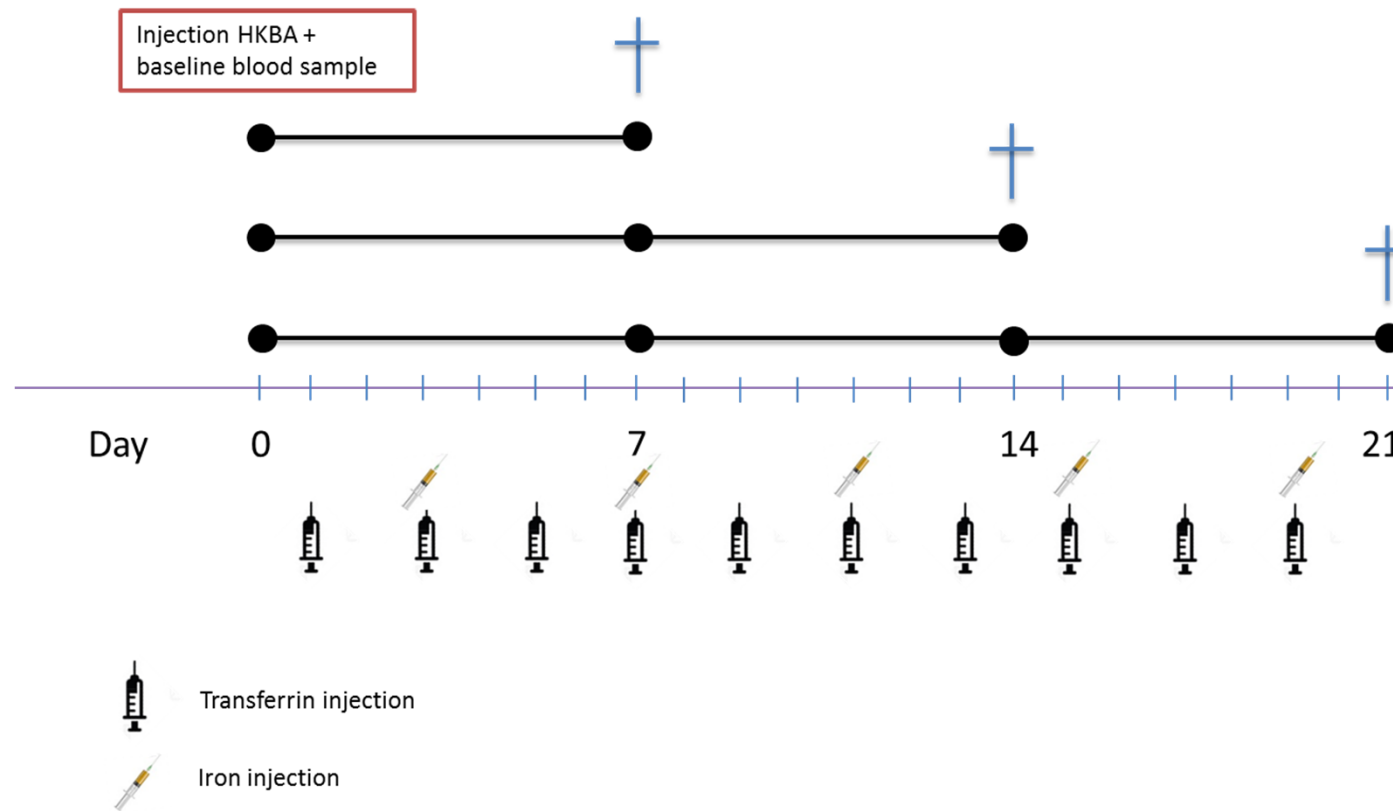
Heat-killed *Brucella abortus* mouse model



Kautz et al. Blood 2014

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Heat-killed *Brucella abortus* mouse model



Heat-killed *Brucella abortus* mouse model

Groups

- All mice, receiving saline
- All mice, receiving apotransferrin
- All mice, receiving apotransferrin + iron
- All mice, receiving iron

Outcome

- Blood: Blood count & iron parameters
- Organs: iron content & inflammatory markers & erythrophagocytosis



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MARS consortium



Benjamin Nota



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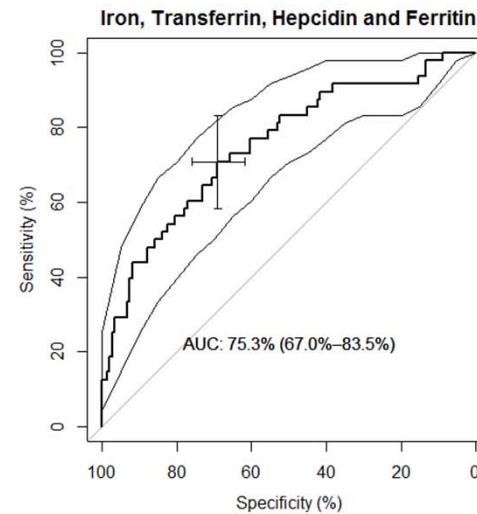
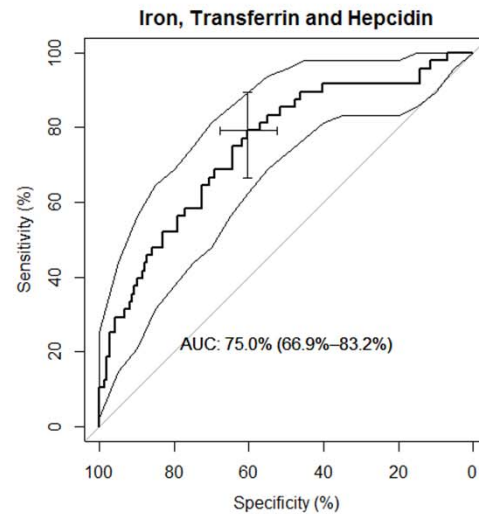
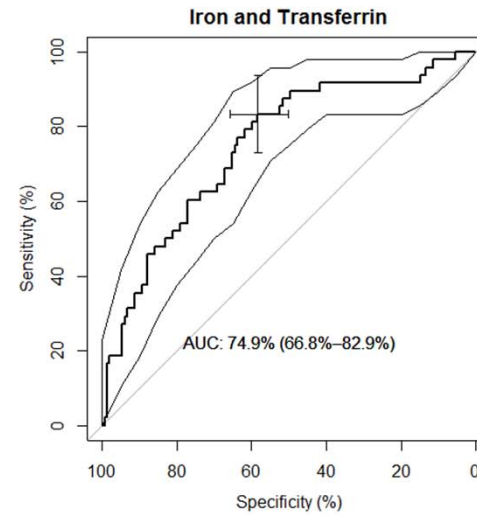
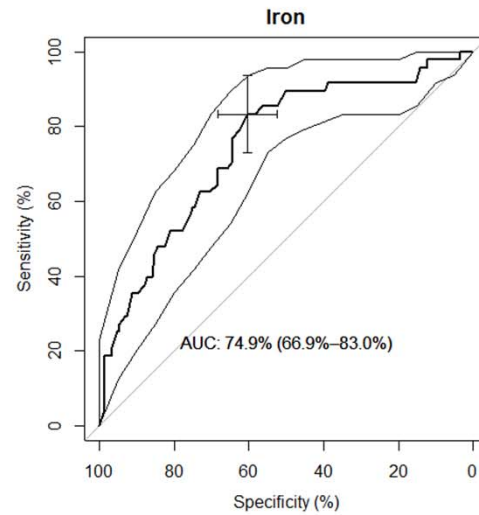
Kirsten van de Groep

Olaf L. Cremer

MARS consortium



Use iron parameters to diagnose AI early?



Iron + Transferrin therapy in AI

