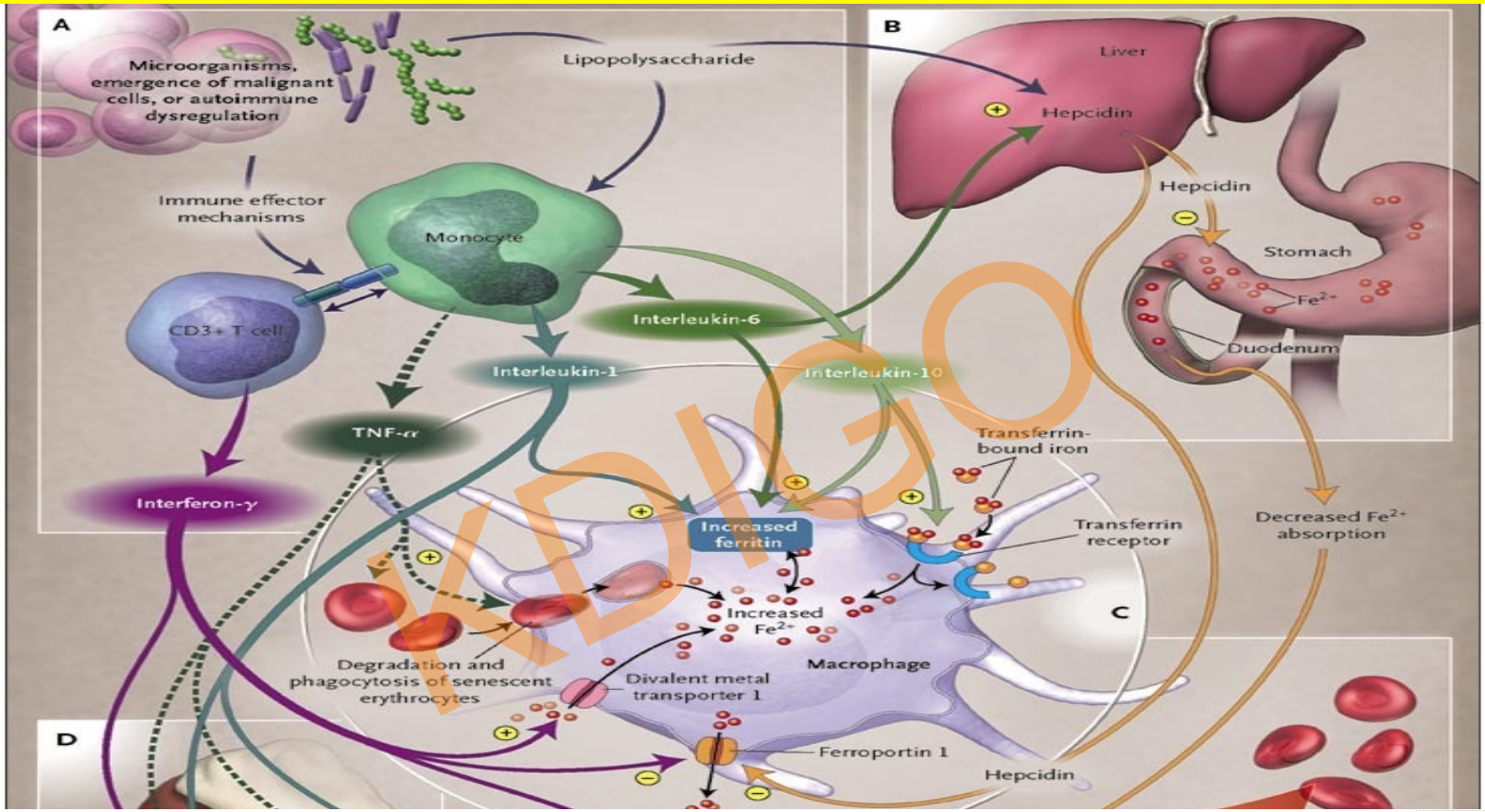
# Iron and Risk of Infection– real or theoretical?





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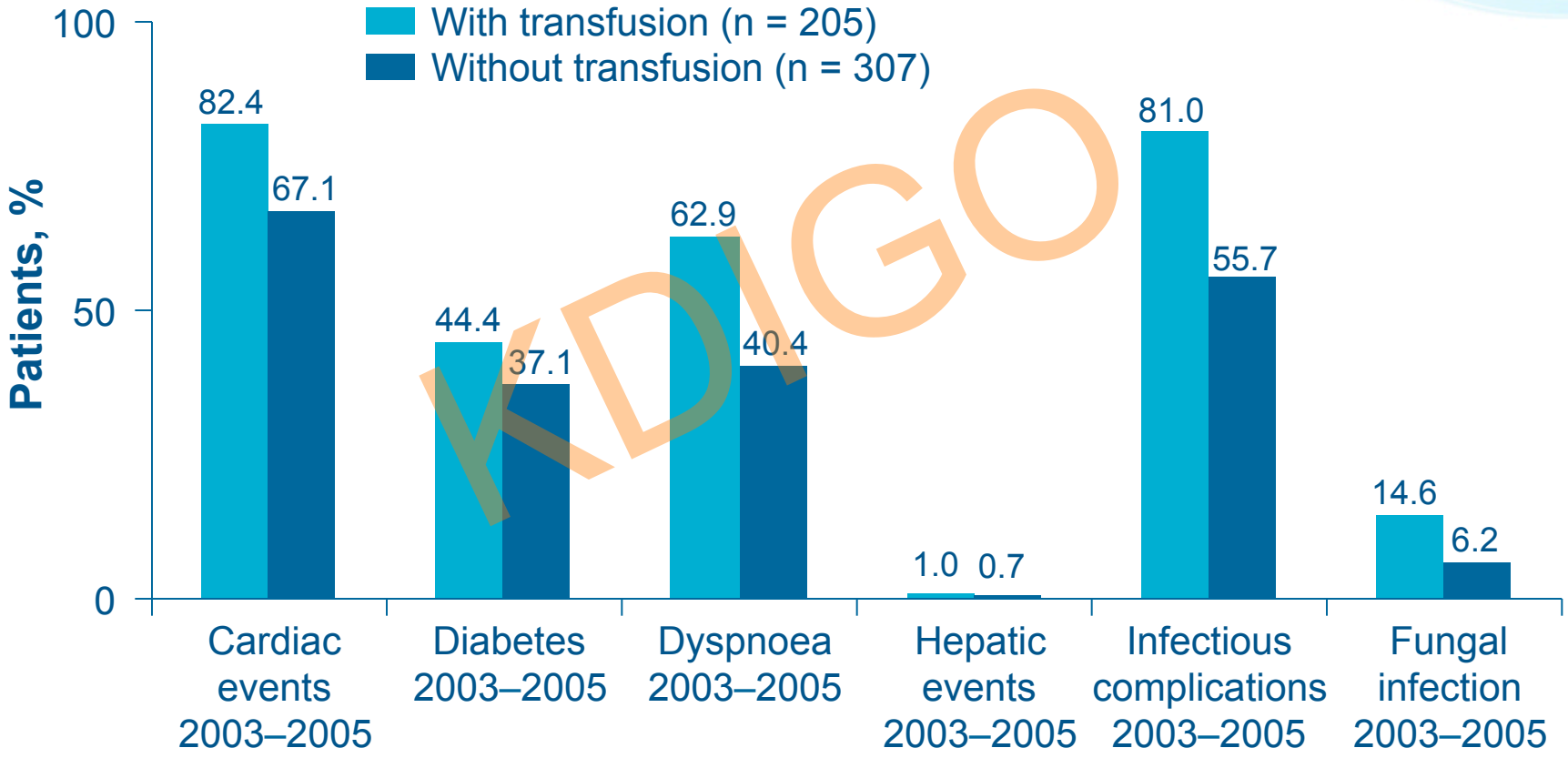
# Infections and their complications are the most prevalent comorbidity in transfusion-dependent MDS



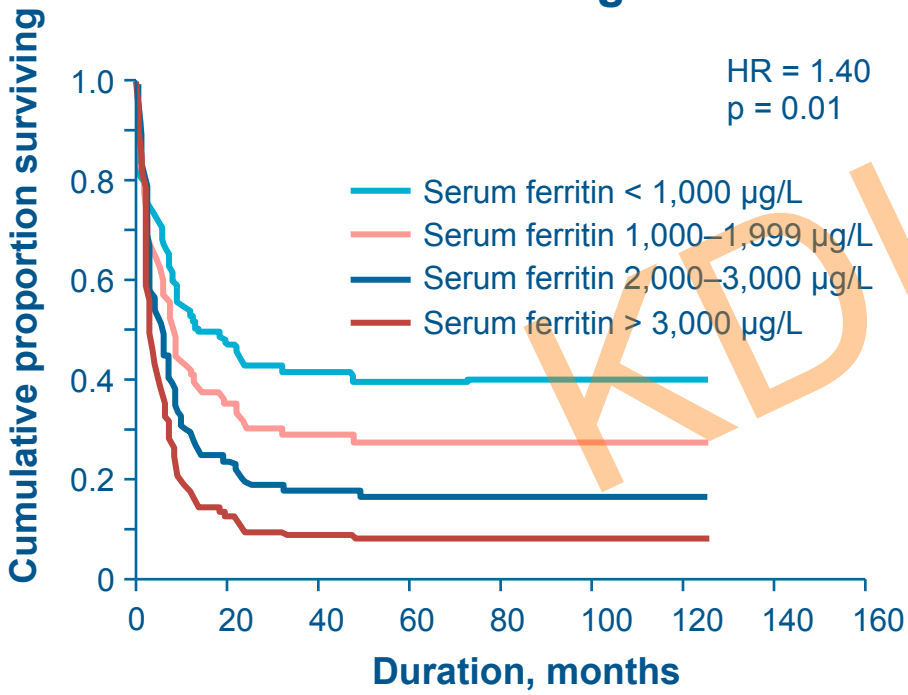


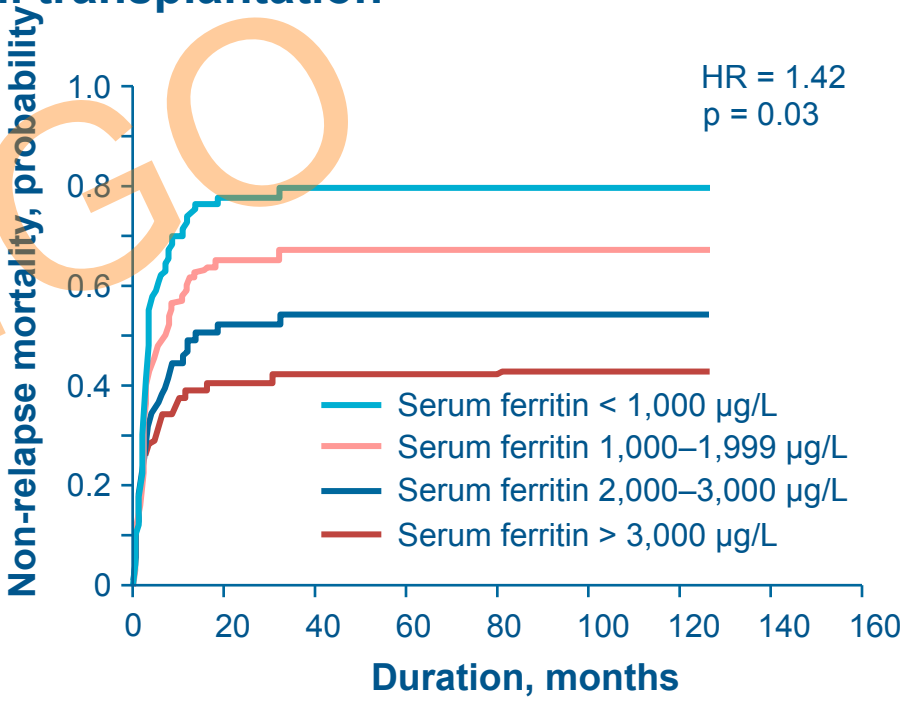

**Transfused MDS patients have a higher prevalence of cardiac events, diabetes mellitus, dyspnoea, and hepatic and infectious diseases than non-transfused MDS patients**

Goldberg SL, et al. J Clin Oncol. 2010;28:2847-52.

# Non-relapse mortality (incl. infections) increases with pre-transplant serum ferritin level

## Survival and non-relapse mortality in MDS patients undergoing allogeneic stem cell transplantation






**Overall survival by serum ferritin level before SCT**

**Non-relapse mortality by serum ferritin level before SCT**

SCT, stem cell transplantation.

Alessandrino EP, et al. Haematologica. 2010;95:476-84.

# Increased tissue iron stores (MRI) but not ferritin levels predict an increase of non disease related mortality in patients after bone marrow transplantation

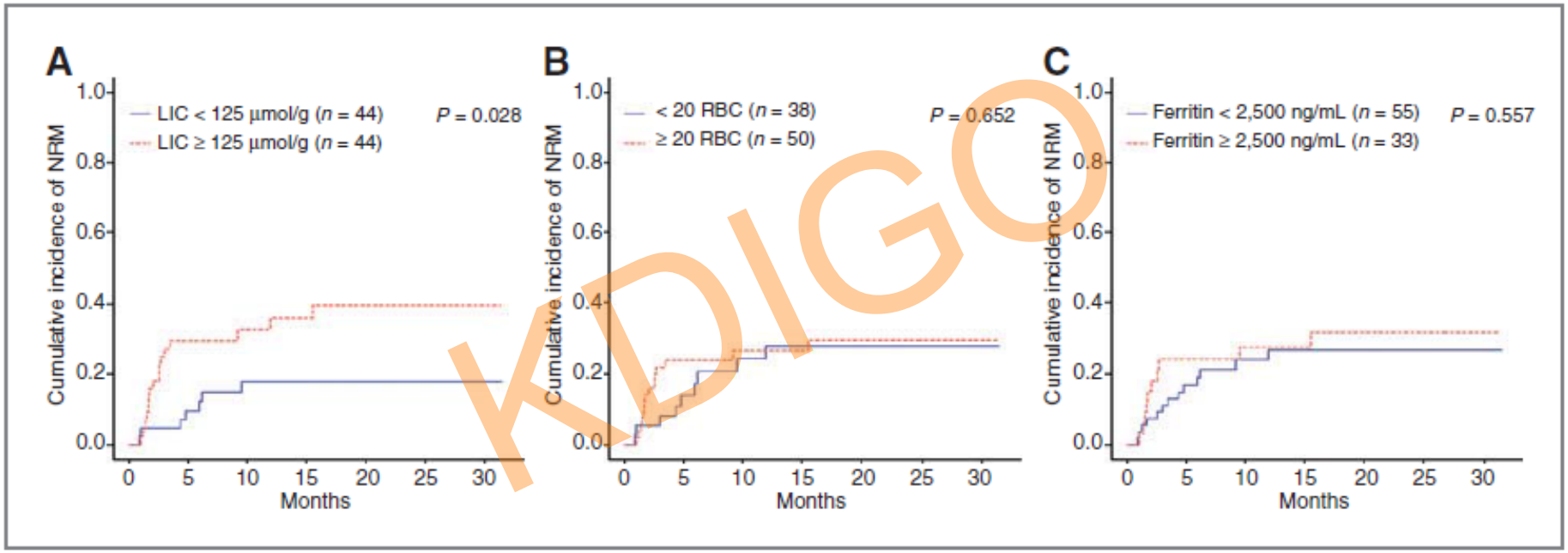





Figure 2. Cumulative incidence of NRM. Cumulative incidence with respect to LIC is given in A, whereas transfusion burden and ferritin are used as grouping variables in B and C. Competing events statistics were used to calculate the incidences and significance.

Wermke et al. Clin Canc Res 2012

# Increased liver iron content (LIC) is linked to increased NDR mortality in HSCT- patients

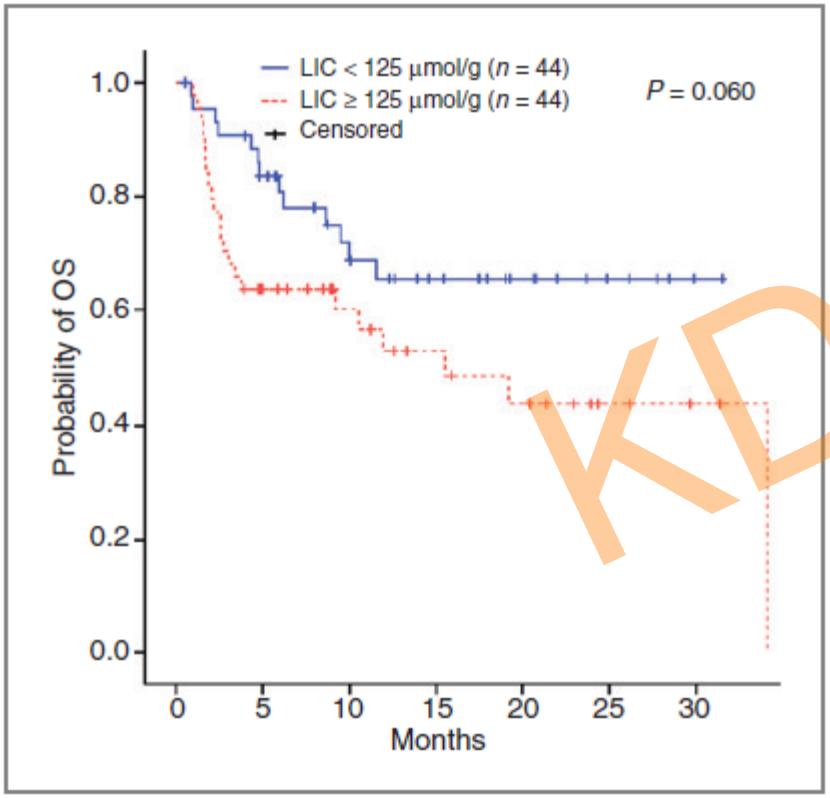



Figure 3. Kaplan–Meier plot of the probability of OS with respect to LIC. Significance was calculated using the log-rank test.

**Table 2.** Multivariate competing risk regression analysis for factors with potential influence on NRM

| | HR | P |
|---|---|---|
| LIC (≥125 µmoL/g vs. <125 µmoL/g) | 2.98 (1.23–7.22) | **0.016** |
| Donor (MUD vs. MRD) | 2.98 (0.81–11.1) | 0.100 |
| HCT-CI | 1.19 (1.00–1.42) | *0.055* |
| Age | 1.00 (0.96–1.04) | 0.980 |
| Time diagnosis to allo-SCT | 0.98 (0.95–1.01) | 0.130 |
| Conditioning (CIC vs. RIC) | 0.44 (0.12–1.55) | 0.200 |
| Disease stage (advanced vs. early) | 0.45 (0.188–1.08) | *0.074* |

NOTE: HCT-CI, age, and time from diagnosis to allo-SCT were entered as continuous variables. Bold, $P < 0.05$; italic, $P < 0.1$.



Wermke et al. Clin Canc Res 2012

# Higher ferritin levels are assocaited with increased risk of infection in Kidney Tx patients

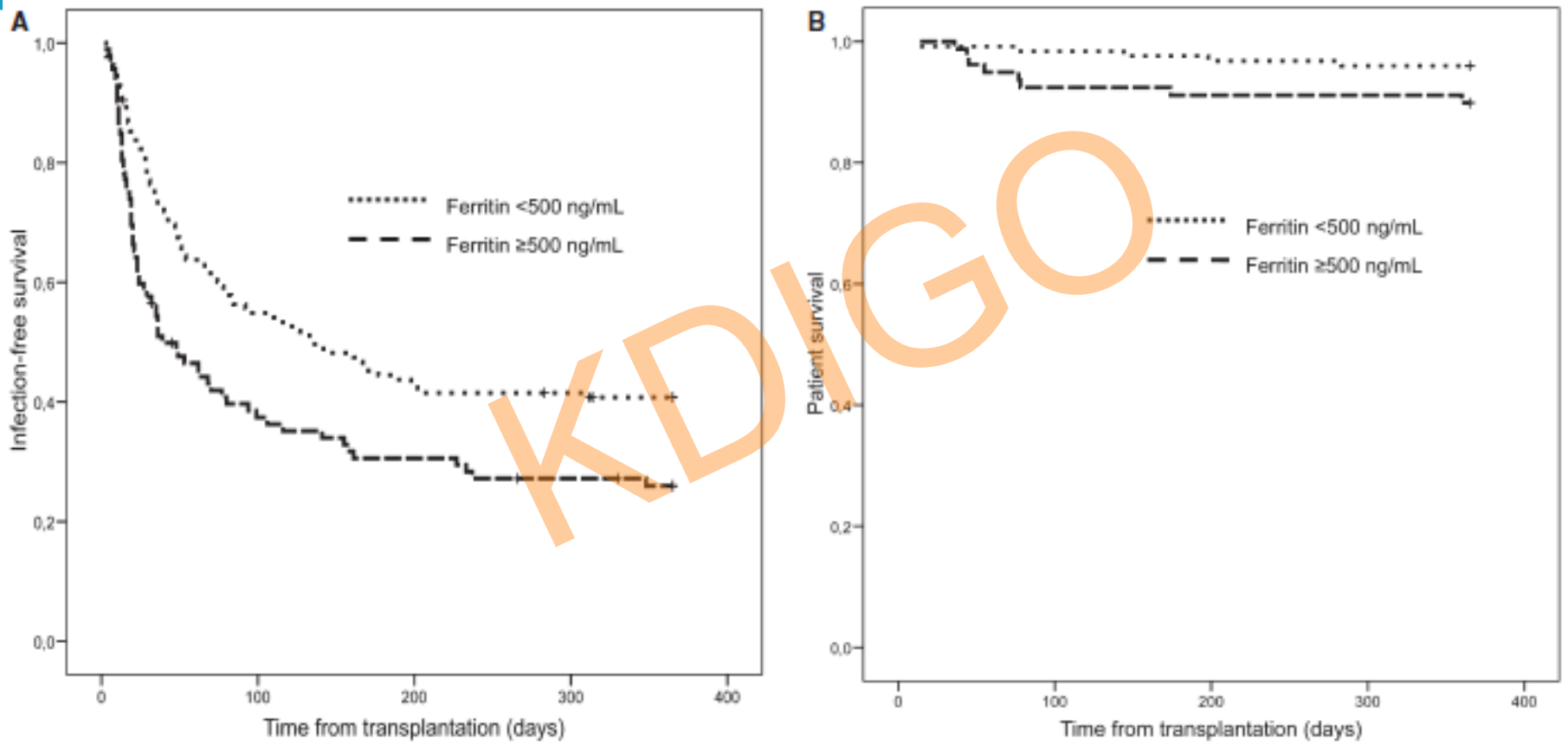





*Fig. 2.* Kaplan–Meier curves during the first post-transplant year stratified by serum ferritin levels: (A) infection-free survival (log-rank test; $P = 0.004$); (B) patient survival (log-rank test; $P = 0.105$).

Fernandez-Ruiz et al NDT 2013

# Association between serum ferritin and risk of infection in dialysis patients

**TABLE 1. Association between serum ferritin and infection and infection-related mortality in hemodialysis patients**

| Author/Year | Country/No. of centers | N[a] | Predictor(s) | Outcome(s) | Results[b] | Summary |
|---|---|---|---|---|---|---|
| ***Association between serum ferritin and infection or infection-related mortality*** | | | | | | |
| Seifert 1987 (53) | Germany 2 centers | 184 | Mean SF during study period: 10–330, 331–1000 or 1001–2000 ng/ml | Bacterial infections (BIs)/ patient-year (PY) where BI includes septicemia and other BIs | 0.34 BIs/PY (SF 331–1000 ng/ml) vs. 0.18 BIs/PY (SF 10–330 ng/ml), $p < 0.05$. 0.59 BIs/PY (SF 1001–2000 ng/ml) vs. 0.18 BIs/PY (SF 10–330 ng/ml), $p < 0.01$. | Higher rates of BI were observed in the higher SF groups. |
| Boelaert 1987 (54) | Belgium 36 centers | 1421 | SF at time of questionnaire: <500 or >500 ng/ml | Proportion with *Yersinia enterocolitica* bacteremia (YEB) in the previous 5 years | 0.93% YEB (SF >500 ng/ml) vs. 0% YEB (SF <500 ng/ml), $p < 0.05$. | A higher proportion of previous YEB was observed in the higher SF group. |
| Tielemans 1989 (55) | Belgium 1 center | 61 | Mean SF during study period: ≤500 or >500 ng/ml | Bacterial infections (BIs)/ patient-year (PY) where BI includes septicemia and other BIs; time to first BI | 0.48 BIs/PY (SF >500 ng/ml) vs. 0.09 BIs/PY (SF ≤500 ng/ml), $p < 0.001$. Shorter time to first BI with higher ferritin, $p < 0.005$ (logrank). | A higher rate of BI and shorter time to BI were observed in the higher SF group. |
| Boelaert 1990 (56) | Belgium 1 center | 158 | SF classified every 3 months: <500, 500–1000, or >1000 ng/ml (<500 and 500–1000 ng/ml combined for analysis) | Bacteremic episodes (BEs)/ patient-year (PY) | 0.34 BEs/PY (SF >1000 ng/ml) vs. 0.12 BEs/PY (SF ≤1000 ng/ml), $p < 0.005$. | A higher rate of BEs was observed in the higher SF group. |
| Hoen 1995 (57) | France 13 centers | 607 | SF at first bacterial infection (BI) or end of study period if no BI: <500 or ≥500 ng/ml | Bacterial infection (BI) over 6-month period | OR for BI (SF ≥500 vs. <500 ng/ml): 1.79 (95% CI 1.06–3.00). | Higher SF was independently associated with higher odds of BI. |
| Teehan 2004 (58) | US 1 center | 87 | Iron deficiency (TSAT <20% and SF <100 ng/ml), functional iron deficiency (TSAT <20% and SF >100 ng/ml), iron replete (TSAT >20% and SF >100 ng/ml). Measured at baseline prior to initiation of IV iron. (Iron deficiency and functional iron deficiency combined for analysis.) | Proportion with bacterial infection (BI), which included bacteremia or bacterial pneumonia, and time to BI over 2 years | Higher proportion of BI in iron replete (56%) than functionally iron deficient (27%) or iron deficient (37%) groups. HR for BI (iron replete vs. non-iron replete): 3.1 (95% CI 1.4–6.8). | Iron repletion was independently associated with higher hazard of BI. |
| Teehan 2004 (28) | US 2 centers | 132 | Iron deficiency (TSAT <20% and SF <100 ng/ml), functional iron deficiency (TSAT <20% and SF ≥100 ng/ml), iron replete (TSAT ≥20% and SF ≥100 ng/ml). Based on mean values within 3 months of starting IV iron. (Iron deficiency and functional iron deficiency combined for analysis.) | Proportion with bacteremia and time to first bacteremic episode over 1 year | Proportion with bacteremia in iron replete (35%) vs. non-iron replete (18%), $p$ 0.06. HR for bacteremia (iron replete vs. non-iron replete): 2.5 (95% CI 1.1–5.7). | Iron repletion was independently associated with higher hazard of bacteremia. |



Ishida et al. Seminars in Dialysis 2014

# Association between serum ferritin and risk of bacterial infection in dialysis patients– cont.

**Table 1.** (Continued)

| Author/Year | Country/No. of centers | N[a] | Predictor(s) | Outcome(s) | Results[b] | Summary |
|---|---|---|---|---|---|---|
| Jenq 2009 (11) | Taiwan 3 centers | 187 | Baseline SF (measured during first week of study, ng/ml) | Infection-related mortality (IRM) at 1 year | HR for IRM: 1.001 per 1 ng/ml (95% CI 1.000–1.002) or 1.5 per 500 ng/ml. | Higher SF was independently associated with higher hazard of IRM. |
| Galic 2011 (13) | Bosnia & Herzegovina 1 center | 120 | SF (time of ascertainment not specified): ≤500 or >500 ng/ml | Proportion with sepsis and vascular access infection (VAI) at 18 months | 61.9% with sepsis (SF >500 ng/ml) vs. 27.3% with sepsis (SF ≤500 ng/ml), $p$ 0.005. 45.5% with VAI (SF >500 ng/ml) vs. 5.1% with VAI (SF ≤500 ng/ml), $p < 0.001$. | Higher proportions with sepsis and VAI were observed in the higher SF group. |
| ***No association between serum ferritin and infection or infection-related mortality*** | | | | | | |
| Hoen 1998 (26) | France 19 centers | 985 | Baseline SF (ng/ml) | Bacteremia over 6-month period | $p > 0.2$ for association of SF with bacteremia. | SF was not significantly associated with hazard of bacteremia. |
| Nurko 1999 (60) | US Medicare database | 2662 | SF (time of ascertainment not specified) | Infection-related mortality (IRM) at 2 years | No numerical data provided. | SF was not significantly associated with hazard of IRM. |
| Jean 2002 (59) | France 1 center | 89 (129 TCs) | Mean SF within 2 months prior to study initiation: ≤500 or >500 ng/ml | Bacteremia-free TC survival | $p$ 0.2 (logrank) for comparison of bacteremia-free TC survival curves for SF >500 and ≤500 ng/ml. | Higher SF was not significantly associated with TC bacteremia (i.e., failed bacteremia-free TC survival). |
| Pollak 2009 (12) | US 3 centers | 1418 | SF <600 vs. >600 ng/ml | Proportion with infection, pneumonia, or cellulitis/ carbuncle | SF >600 vs. <600 ng/ml: % with infection (48.1% vs. 46.1%, $p$ 0.8), pneumonia (17.6% vs. 20.2%, $p$ 0.2), cellulitis/carbuncle (13.5% vs. 12.3%, $p$ 0.6). | Higher SF was not significantly associated with proportion of infection, pneumonia or cellulitis/carbuncle. |

SF, serum ferritin (ng/ml equivalent to μg/l); TSAT, transferrin saturation; IV, intravenous; OR, odds ratio; HR, hazard ratio; CI, confidence interval; TC, tunneled catheter.
[a]Includes sample size with serum ferritin available or included in risk factor analysis if this information was provided.
[b]In some cases, rates and percentages were derived from the results reported in studies in order to standardize units and for ease of interpretation.





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# Iron at the host–pathogen interface

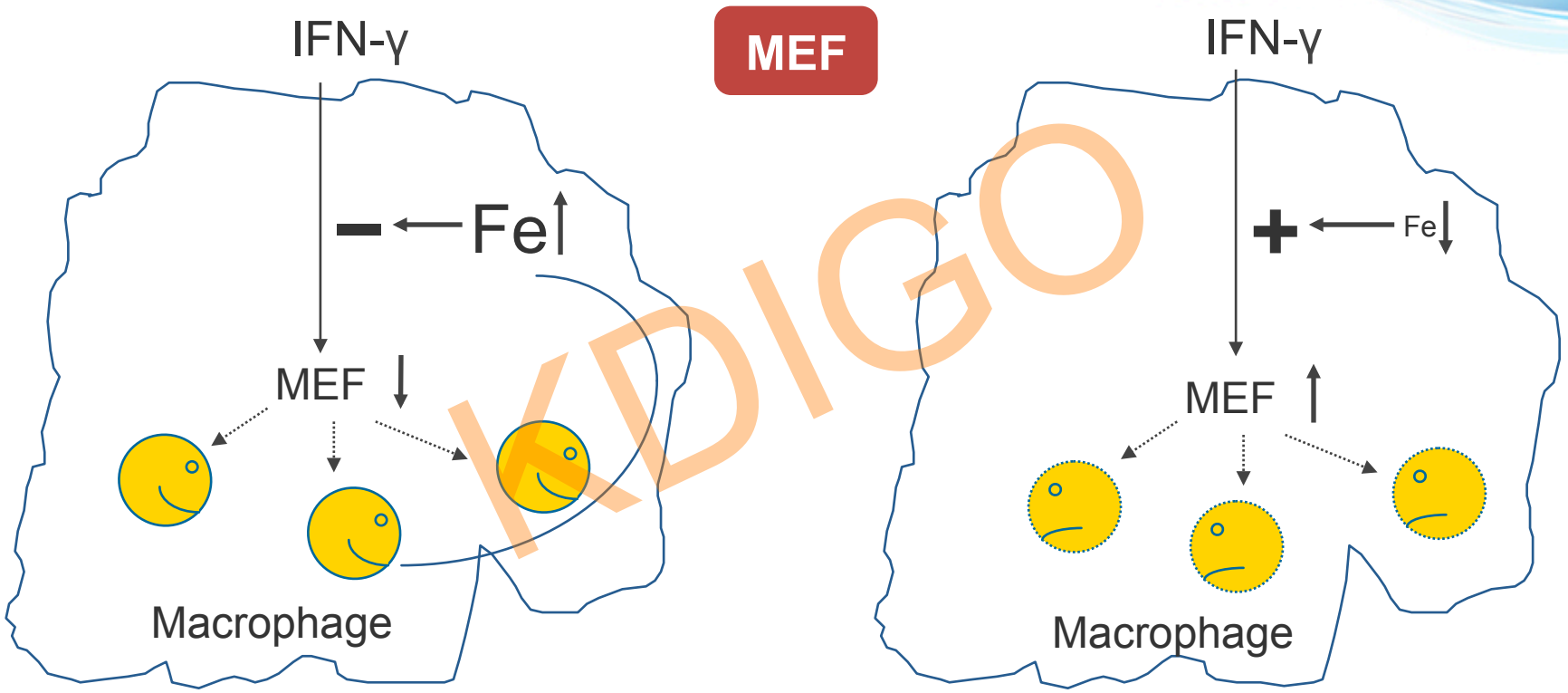
- Essential for growth and proliferation of several microbes
- Expression of iron acquisition and siderophore systems is linked to microbial pathogenicity

Exerts subtle effects on cell-mediated immunity in vitro (macrophage effector pathways, IFN-γ activity, iNOS expression)

**Control of iron homeostasis may be important in the course of an infection**

IFN-γ, interferon-gamma; iNOS, inducible nitric oxide synthase.

# Iron loading impairs macrophages' ability to kill intracellular pathogens



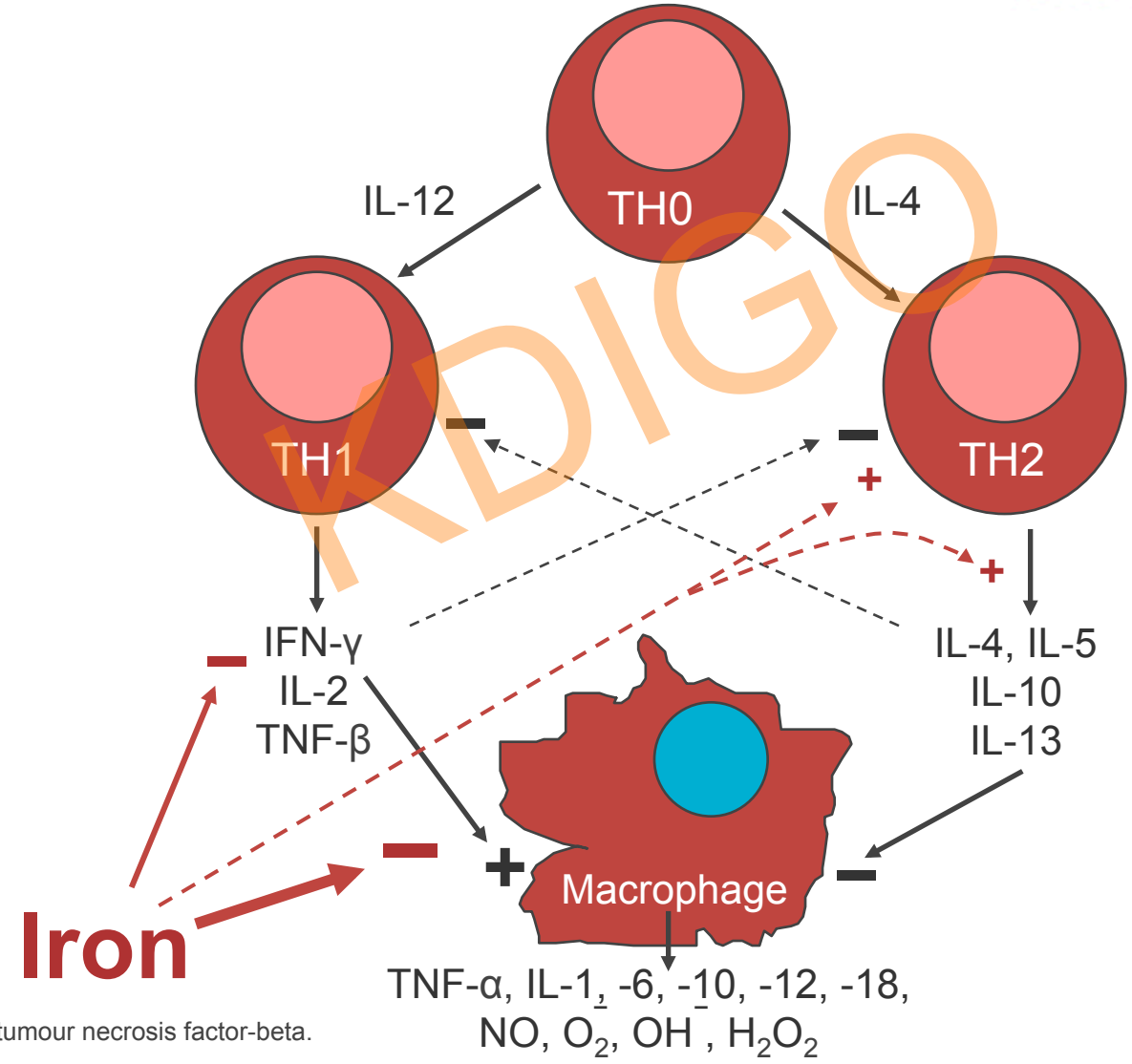



**Iron overload also negatively affects neutrophil function and phagocytosis**

Bellmann-Weiller et al. Immunobiology 2010 and 2013; Fritsche G, et al. J Infect Dis. 2001;183:1388-94. Fritsche G, et al. J Immunol. 2003;171:1994-8. Mair SM, et al. J Infect Dis. 2011;204:685-94. Oexle H, et al. J Leukoc Biol. 2003;74:287-94. Weiss G, et al. Exp Hematol. 1992;20:605-10. Weiss G, et al. EMBO J. 1993;12:3651-7. Weiss G, et al. J Exp Med. 1994;180:969-76. Weiss G, et al. Immunol Today. 1995;16:495-500. Weiss G, et al. J Infect Dis. 1997; 1998,1999,2001; Nairz et al. Cell Microbiol 2007 and 2009, Eur J Immunol 2008;

MEF, macrophage effector function.

# Iron alters the TH1–TH2 balance

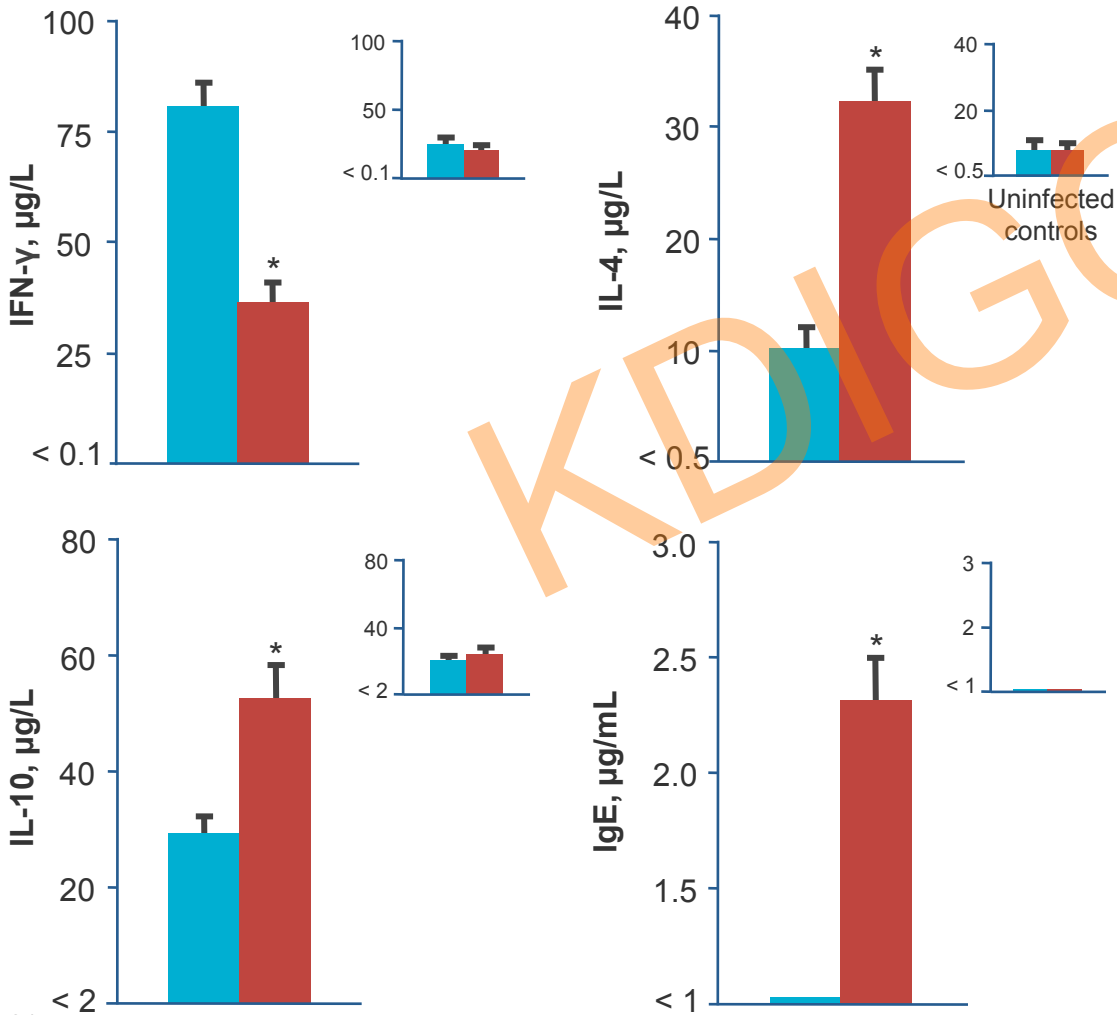





IL, interleukin; TNF-β, tumour necrosis factor-beta.

Weiss et al. Immunol.Today 1995

# Iron overload alters the TH1–TH2 immune response




**The protective TH1-mediated immune response was reduced in iron-overloaded mice infected with *Candida albicans***



* $p < 0.01$.
IL, interleukin; TH, T-helper (cell).

Mencacci A, et al. J Infect Dis. 1997;175:1467-76.

# Effect of iron and zinc supplementation on health in children in Pakistan

Prospective comparative study with approx. 900 children in each group
(No supplement and iron Suppl. with/without zinc)

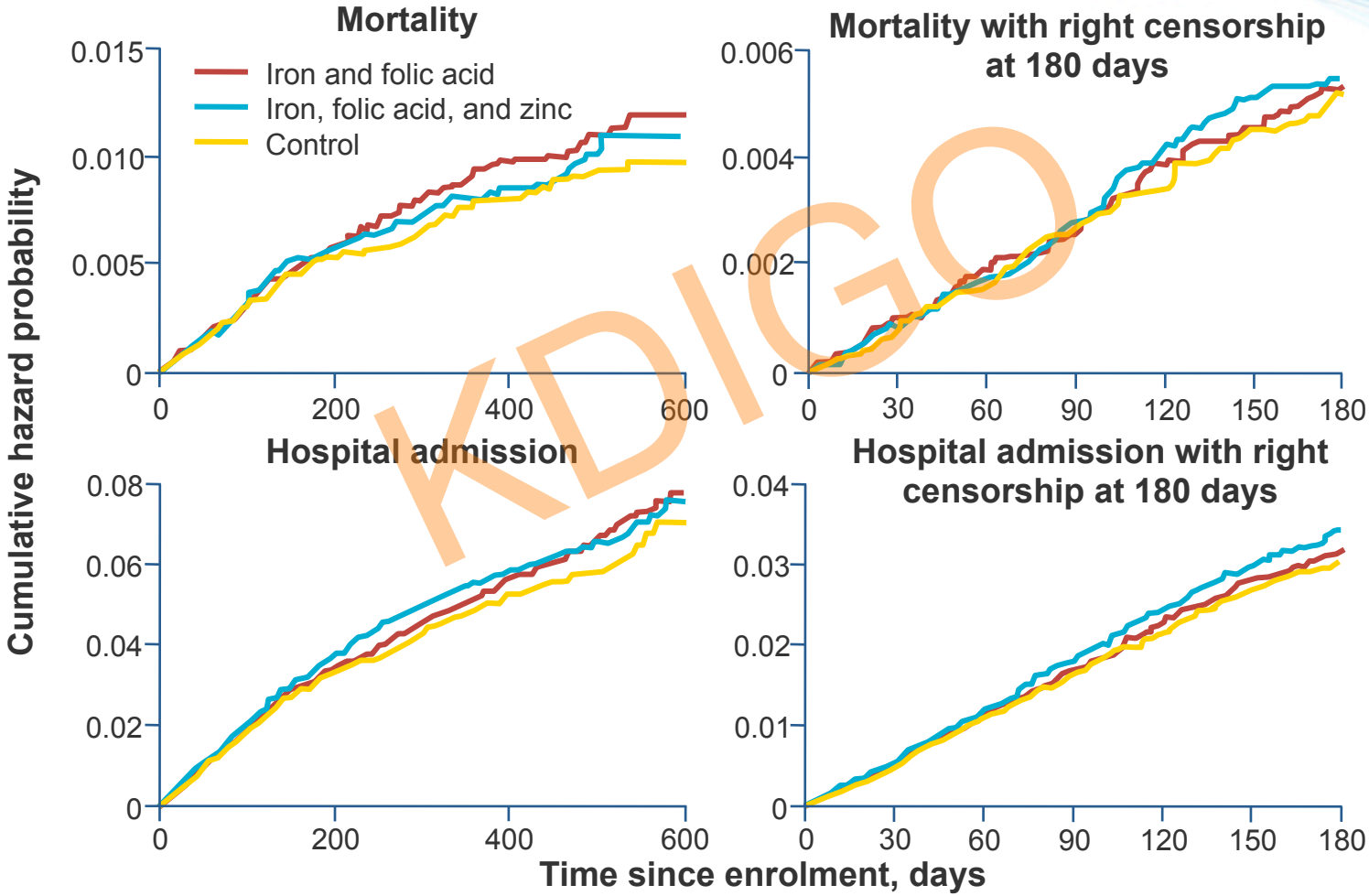


an extra 0·56 cm (0·29–0·84). We recorded strong evidence of an increased proportion of days with diarrhoea (p=0·001) and increased incidence of bloody diarrhoea (p=0·003) between 6 and 18 months in the two micronutrient powder groups, and reported chest indrawing (p=0·03). Incidence of febrile episodes or admission to hospital for diarrhoea, respiratory problems, or febrile episodes did not differ between the three groups.

**Interpretation** Use of micronutrient powders reduces iron-deficiency anaemia in young children. However, the excess burden of diarrhoea and respiratory morbidities associated with micronutrient powder use and the very small effect on growth recorded suggest that a careful assessment of risks and benefits must be done in populations with malnourished children and high diarrhoea burdens.

Soofi et al. LANCET 2013

# Dietary iron supplementation increases mortality in children in Eastern Africa



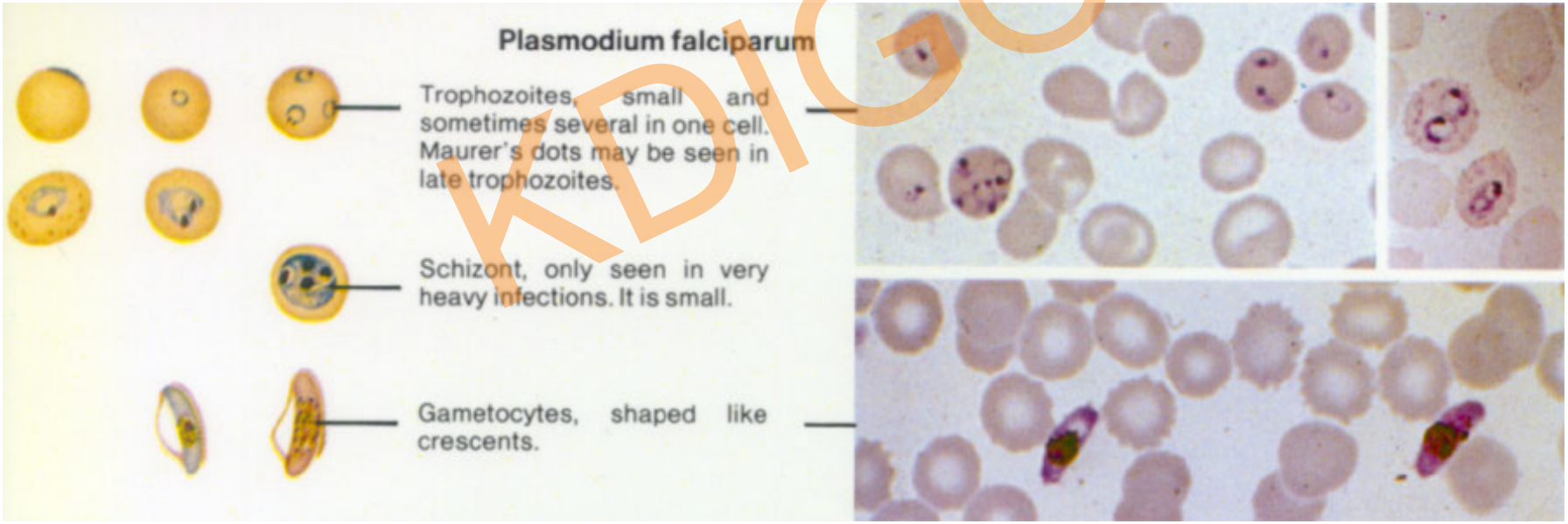



**Children who received iron and folic acid with or without zinc were 12% more likely to die (p = 0.02)**

Sazawal S, et al. Lancet. 2006;367:133-43.

# Iron deficiency protects from malaria and decreases the incidence of subsequent malaria episodes

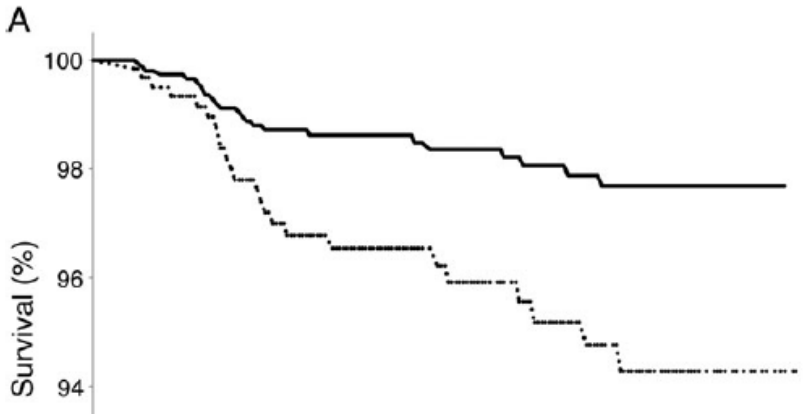
- Prospective study with 785 children in Tanzania enrolled at birth



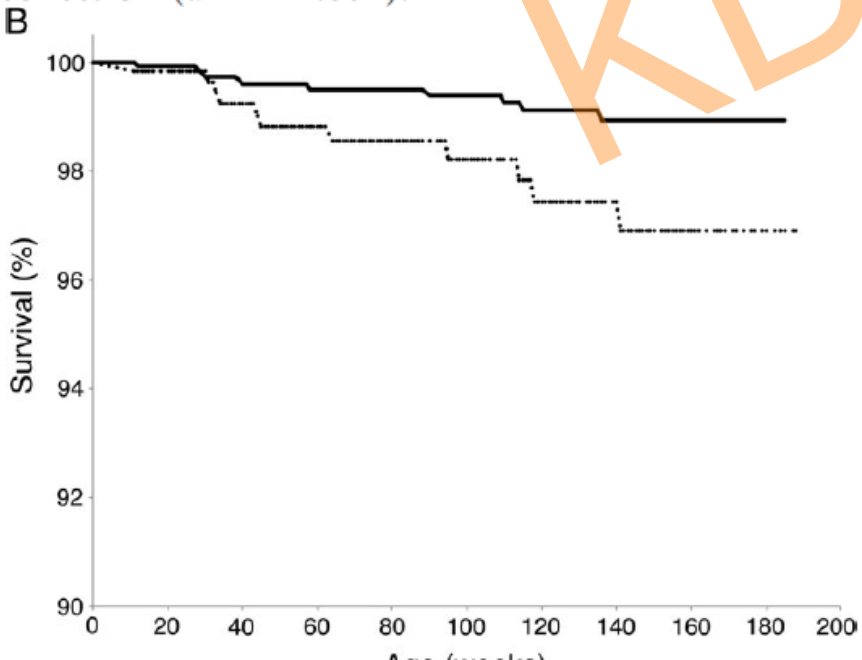



Gwamaka et al. J Infect Dis 2012

# Iron deficiency decreases all-cause (A) and malaria associated mortality (B) in children




***Results.*** ID at routine, well-child visits significantly decreased the odds of subsequent parasitemia (23% decrease, $P < .001$) and subsequent severe malaria (38% decrease, $P = .04$). ID was also associated with 60% lower all-cause mortality ($P = .04$) and 66% lower malaria-associated mortality ($P = .11$). When sick visits as well as routine healthy-child visits are included in analyses (average of 3 iron status assays/child), ID reduced the prevalence of parasitemia (6.6-fold), hyperparasitemia (24.0-fold), and severe malaria (4.0-fold) at the time of sample collection (all $P < .001$).






Gwamaka et al. J Infect Dis 2012

# Some infections affected by iron perturbations

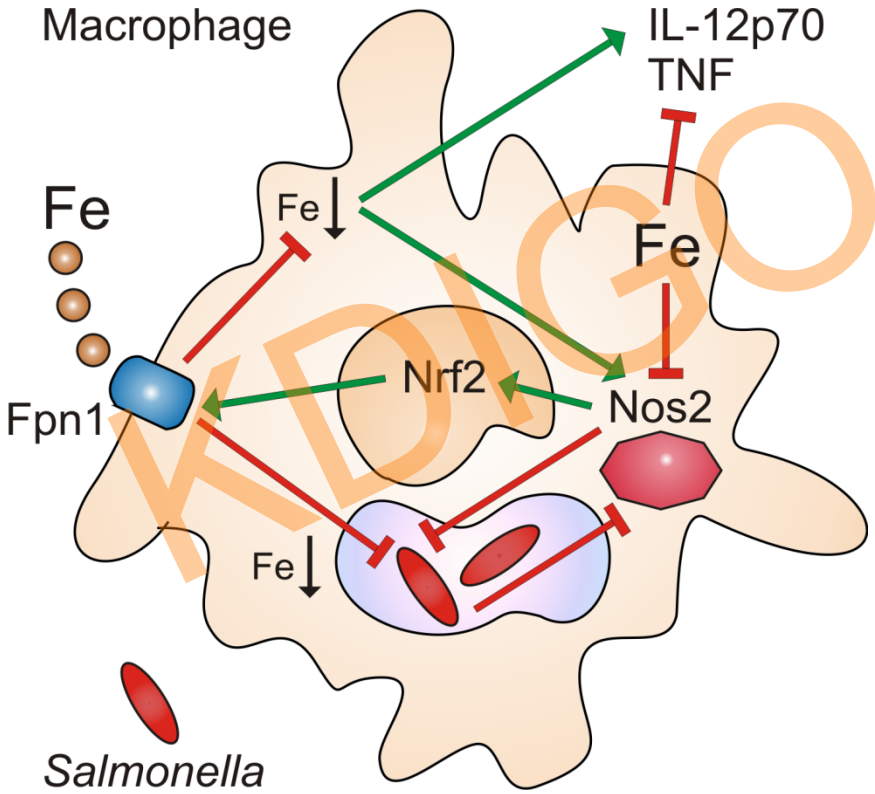
- **Viral**
  - hepatitis C: iron impairs TH1-mediated immune effector pathways against HCV,[1] impairs the clinical response to IFN-α,[2] and stimulates HCV translation[3]
  - HIV: there is a negative association between iron status and HIV progression[4]
- **Fungal**
  - *Aspergillus fumigatus*: expression of fungal iron uptake systems and iron availability are linked to pathogenicity[5]
  - *Candida* infection in mice is negatively affected by iron[6]
- **Bacterial**
  - *Mycobacterium tuberculosis* and *Salmonella typhimurium*: negative effect of iron on disease progression and immune function[7]
  - treatment of staphylococci with lactoferrin



1. Weiss G, et al. J Infect Dis. 1999;180:1452-8. 2. Pietrangelo A. Gastroenterology. 2003;124:1509-23.
3. Theurl I, et al. J Infect Dis. 2004;190:819-25. 4. Gordeuk VR, et al. J Clin Virol. 2001;20:111-5.
5. Schrettl M, et al. J Exp Med. 2004;200:1213. 6. Mencacci A, et al. J Infect Dis. 1997;175:1467-76.
7. Fritsche G, et al. J Immunol. 2003;171:1994-8.

# INNATE RESISTANCE MECHANISMS PROTECT FROM INTRACELLUALR INFECTION BY AFFECTING MICROBIAL IRON AVAILABILITY

NO produced by NOS2 inhibits central metabolic pathways in *Salmonella* directly and also activates Fpn1-mediated iron export via Nrf2.



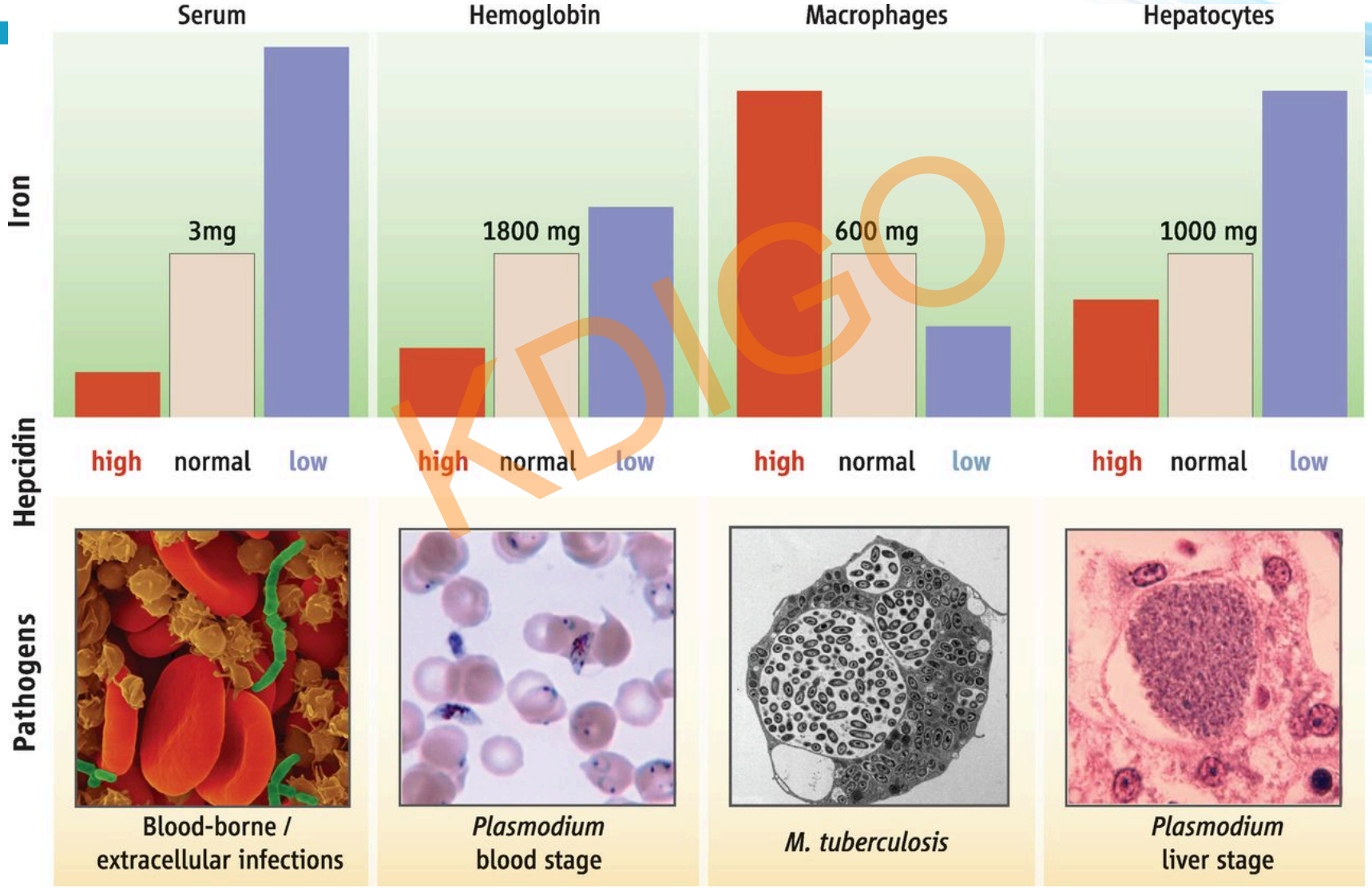

The subsequent reduction of intracellular iron levels restricts the availability of iron to intracellular microbes and enhances TNF-α and IL-12 production.



Nairz et al. J Exp Med. 2013

# Iron metabolism is differently handled according to the location of the pathogen

**High hepcidin is protective in infections with extracellular pathogens versus low hepcidin (FP-1 mediated iron egress) is beneficial in infection with intracellular pathogens**






H Drakesmith, and A M Prentice Science 2012;338:768-772

# Iron therapy in dialysis patients

Prospective study investigating the incidence of infectious complications in ESDR patients receiving i.v. iron therapy

Group 1: ferritin< 100ng/ml and TfS <20%

Group 2: ferritin> 100ng/ml and TfS >20%

Observation-period: one year



Frequency of sepcticemia in group 2 was 2.5-fold higher than in group 1

Too much iron may be harmful in ACD!

Teehan et al. Clin Infect Dis;2004.

# Meta-analysis – Effects of IRON Therapy

- Systemic analysis of randomized controlled trials between 1966 and 2012
- 72 studies including 10 605 patients provided quantitative outcome data for meta-analysis.

- Intravenous iron was associated with an increase in haemoglobin concentration and a reduced risk of requirement for red blood cell transfusion

- Intravenous iron was, however, associated with a significant increase in risk of infection (relative risk 1.33, 95% confidence interval 1.10 to 1.64) compared with oral or no iron supplementation. The results remained similar when only high quality trials were analysed.

Litton et al. BMJ 2013

# Bolus versus maintenance iron dosing in ESRD patients

- retrospective cohort study of hemodialysis patients to compare the safety of bolus dosing with maintenance dosing
- Using clinical data from 117,050 patients of a large US dialysis provider (776,203 exposure/follow-up pairs)
- Follow up three month
- 13% involved bolus dosing, 49% involved maintenance dosing, and 38% did not include exposure to iron



Brookhart et al. J Am Soc Nephrol 24: 1151–1158, 2013.

# Bolus versus maintenance iron dosing in ESDR Patients

Table 2. HRs and RDs for high versus low dose and bolus versus maintenance dosing comparisons

| Parameter Estimate (95% CI) | High Versus Low Dose | | | Bolus Versus Maintenance Dosing | | |
|---|---|---|---|---|---|---|
| | Hospitalized for Infection | Infection-Related Death | Infection-Related Hospitalization or Death | Hospitalized for Infection | Infection-Related Death | Infection-Related Hospitalization or Death |
| Unadjusted HR | 1.37 (1.33 to 1.40) | 1.43 (1.32 to 1.55) | 1.37 (1.34 to 1.40) | 1.51 (1.47 to 1.56) | 1.63 (1.48 to 1.78) | 1.52 (1.48 to 1.56) |
| Adjusted HR | 1.05 (1.02 to 1.07) | 1.08 (0.99 to 1.19) | 1.05 (1.02 to 1.08) | 1.08 (1.05 to 1.11) | 1.11 (1.00 to 1.23) | 1.08 (1.05 to 1.11) |
| Adjusted RD/1000 person-yr | 12.1 (5.7 to 18.8) | 1.2 (−0.74 to 2.8) | 13.0 (6.2 to 19.5) | 24.8 (15.8 to 33.1) | 2.0 (−0.36 to 4.1) | 26.1 (17.6 to 35.0) |

Adjusted analyses controlled for the following variables at baseline: age; race; sex; vintage; number of hospital days in the last month; history of infection in the last month; BMI; most recent vascular access; hemoglobin; ferritin; index TSAT; iron dose; albumin level; EPO dose; history in the last 6 months of pneumonia, sepsis, vascular access infection, diabetes, stroke, MI, chronic obstructive pulmonary disease, cancer, or GI bleeding; and EPO dose during exposure ($n$=776,203).

Table 3. HRs and RDs for high versus low and bolus versus maintenance dosing comparisons using expanded definitions of infection

| Parameter Estimate (95% CI) | Hospitalized for Infection of Any Organ System | | Use of IV Antibiotics | | Hospitalized for Infection or Use of IV Antibiotics | |
|---|---|---|---|---|---|---|
| | High Versus Low | Bolus Versus Maintenance | High Versus Low | Bolus Versus Maintenance | High Versus Low | Bolus Versus Maintenance |
| Unadjusted HR | 1.32 (1.30 to 1.35) | 1.44 (1.41 to 1.47) | 1.24 (1.22 to 1.27) | 1.34 (1.32 to 1.37) | 1.27 (1.25 to 1.28) | 1.37 (1.35 to 1.39) |
| Adjusted HR | 1.03 (1.01 to 1.06) | 1.05 (1.03 to 1.08) | 1.02 (1.00 to 1.03) | 1.05 (1.03 to 1.07) | 1.02 (1.00 to 1.03) | 1.05 (1.03 to 1.07) |
| Adjusted RD/1000 person-yr | 13.9 (4.8 to 24.2) | 27.7 (17.5 to 38.0) | 12.3 (2.7 to 22.9) | 39.8 (27.4 to 53.0) | 18.3 (5.4 to 31.9) | 56.9 (38.3 to 72.5) |

Adjusted analyses controlled for the following variables at baseline: age; race; sex; vintage; number of hospital days in the last month; history of infection in the last month; BMI; most recent vascular access; hemoglobin; ferritin; index TSAT; iron dose; albumin level; EPO dose; history in the last 6 months of pneumonia, sepsis, vascular access infection, diabetes, stroke, MI, chronic obstructive pulmonary disease, cancer, or GI bleeding; and EPO dose during exposure ($n$=776,203).



Brookhart et al. J Am Soc Nephrol 24: 1151–1158, 2013.

# „Iron and infection“ appear to me more complicated

- both severe iron deficiency and iron loading may be of disadvantage

# Association of iron status with failure of anti-tb treatment

| Iron status[a] | # Events/ No. at risk | Unadjusted Model Relative risk (95% CI) | Multivariate Model[b] Relative risk (95% CI) |
|---|---|---|---|
| **Overall** | | | |
| Low | 12/50 | 1.70 (0.94, 3.07) | 1.95 (1.07, 3.52) |
| Normal | 30/212 | 1.00 | 1.00 |
| High | 52/251 | 1.46 (0.97, 2.21) | 1.54 (1.00, 2.39) |
| **HIV-infected patients** | | | |
| Low | 5/22 | 1.82 (0.71, 4.63) | 2.21 (0.96, 5.10) |
| Normal | 12/96 | 1.00 | 1.00 |
| High | 21/141 | 1.19 (0.62, 2.31) | 1.26 (0.63, 2.53) |
| **HIV-uninfected patients** | | | |
| Low | 7/28 | 1.61 (0.75, 3.48) | 1.82 (0.82, 4.05) |
| Normal | 18/116 | 1.00 | 1.00 |
| High | 31/110 | 1.82 (1.08, 3.05) | 1.75 (1.04, 2.95) |

[a]Baseline iron status was categorized as low: plasma ferritin <30 μg/L; normal: plasma ferritin 30 to ≤150 μg/L for women and 30 to ≤200 μg/L for men; and high: plasma ferritin >150 μg/L for women and >200 μg/L for men.

[b]Adjusted risk ratio from a log-binomial regression model adjusting for baseline covariates including sex, age (years), money spent on food per person per day (<500, ≥500 TSH), number of colonies in AFB culture, Karnofsky score (<70%, ≥70%), BMI (kg/m$^2$), history of TB disease (yes/no), HIV infection status, CD4 T cell count (cells/uL) and log HIV RNA (copies/mL), trial regimen and C-reactive protein (mg/L).

*P* value, test for interaction by HIV infection status = 0.55.

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**TABLE 4** Association of hematological status with mortality and HIV disease progression among TB-infected patients in Tanzania[1]

| Hematological status[2] | Events, n/person-mo | Unadjusted model RR (95% CI) | Multivariate model RR (95% CI)[3] |
|---|---|---|---|
| Mortality | | | |
| All patients | | | |
| No anemia or iron deficiency | 38/18,483 | 1.00 | 1.00 |
| Iron deficiency without anemia | 21/6126 | 1.52 (0.89, 2.60) | 2.89 (1.53, 5.47) |
| Anemia without iron deficiency | 52/3194 | 6.98 (4.55, 10.72) | 2.72 (1.50, 4.93) |
| Iron deficiency anemia | 35/4657 | 3.40 (2.13, 5.41) | 2.13 (1.10, 4.11) |
| HIV-infected patients[4] | | | |
| No anemia or iron deficiency | 34/6419 | 1.00 | 1.00 |
| Iron deficiency without anemia | 15/1686 | 1.64 (0.89, 3.00) | 2.78 (1.33, 5.81) |
| Anemia without iron deficiency | 50/2479 | 3.75 (2.41, 5.83) | 2.53 (1.36, 4.68) |
| Iron deficiency anemia | 33/2689 | 2.34 (1.44, 3.80) | 1.99 (1.01, 3.93) |
| HIV-uninfected patients[4] | | | |
| No anemia or iron deficiency | 4/12,064 | 1.00 | 1.00 |
| Iron deficiency without anemia | 6/4441 | 3.82 (1.07, 13.55) | 3.79 (1.04, 13.79) |
| Anemia without iron deficiency | 2/714 | 8.77 (1.60, 48.07) | 6.19 (1.03, 37.08) |
| Iron deficiency anemia | 2/1969 | 3.06 (0.56, 16.71) | 3.81 (0.64, 22.57) |
| HIV progression[5] | | | |
| No anemia or iron deficiency | 26/4698 | 1.00 | 1.00 |
| Iron deficiency without anemia | 13/959 | 2.50 (1.28, 4.91) | 3.72 (1.71, 8.10) |
| Anemia without iron deficiency | 26/1671 | 3.11 (1.78, 5.44) | 3.55 (1.73, 7.31) |
| Iron deficiency anemia | 22/2094 | 1.93 (1.08, 3.45) | 2.99 (1.44, 6.23) |
| HIV progression or death[5] | | | |
| No anemia or iron deficiency | 37/4273 | 1.00 | 1.00 |
| Iron deficiency without anemia | 16/824 | 2.07 (1.15, 3.73) | 3.51 (1.62, 7.59) |
| Anemia without iron deficiency | 46/1495 | 3.77 (2.42, 5.89) | 4.13 (2.07, 8.25) |
| Iron deficiency anemia | 37/1927 | 2.38 (1.49, 3.79) | 3.40 (1.69, 6.86) |

[1] Hb, hemoglobin; MCV, mean corpuscular volume; TB, tuberculosis.

[2] Hematological status was categorized as no anemia or iron deficiency: Hb ≥110 g/L and MCV ≥80 fL; iron deficiency without anemia: Hb ≥110 g/L and MCV <80 fL; anemia without iron deficiency: Hb <110 g/L and MCV ≥80 fL; and iron deficiency anemia: Hb <1 MCV <80 fL.

[3] Adjusted RR from a log-binomial regression model adjusting for sex, age (years via cubic splines), money spent on food (<500, ≥500 Tanzanian shillings spent/person/d), number of colonies in AFB culture (0, 1–100, >100 colonies), Karnfosky score (<70%, ≥70%), BMI (kg/m$^2$ via cubic splines), previous TB disease (yes/no), HIV status, CD4 cell count (cells/mm$^3$ via cubic splines), log HIV RNA (copies/mm$^4$ via cubic splines), malaria infection (yes/no), and trial regimen.



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# Both (severe?) iron deficiency and iron overload exert deterimental effects

mechanisms?

- iron deficiency– impaired immune cell proliferation, malnutrition
- iron overload: inhibition of innate immune function, feeding of pathogens

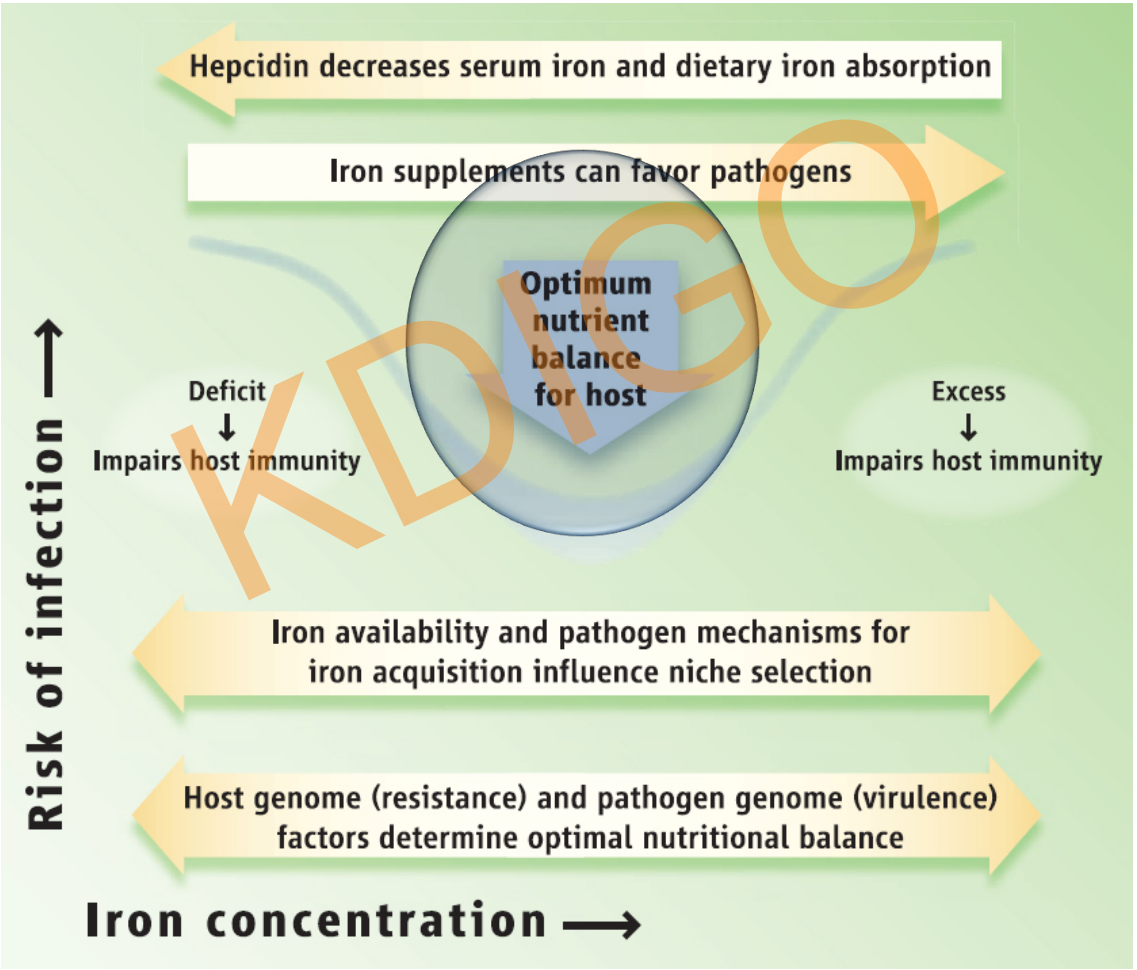
- Different effects depending on the underlying pathogen and specific situation in regard to the risk for infections

- Caveat- definition of: „iron overload“/iron deficiency –

What does an increased ferritin level tell us?

true iron deficiency/loading vs. functional/inflammation driven iron misdistribution vs. Immune exhaustion

# Both iron deficiency and iron loading may be deterimental in infection




*Drakesmith H et al Science 2012*

# Iron therapy and infection

- Iron deficiency appears to be protective in some but deterimental for other infections
- Iron treatment/overload may exacerbate specific chronic infections or increase the susceptibility to infections

- Effect of iron therapy on the course of chronic infections
  - hepatitis C (B?)
  - latent tuberculosis?
  - chronic bacterial infections (joints, lung, katheter)?
  - microbiom– secondary effects?!

# Conclusion

The overall evidence favors an association between iron and infection in hemodialysis patients, but the optimal iron management strategy to minimize infection risk has yet to be identified. There is a need for further research on this topic, particularly in light of increased utilization of intravenous iron following implementation of the bundled ESRD reimbursement system.



Ishida et al. Seminars in Dialysis 2014