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- Pro. Roger is a Consultant Nephrologist at the Renal Unit, Gosford Hospital, Gosford, Australia.
- He now has over 25 years' experience researching anaemia and the role of iron in patients with chronic kidney disease. He lectures widely in this field and has been an invited lecturer at numerous national and international congresses and meetings.
- He has authored or co-authored over 85 journal articles, including papers in the NEJM, JAMA, KI, NDT and AJKD and has contributed to the development of national and international guidelines including CARI Guidelines and the 2008 KDIGO guideline.



IRON DEFICENCY/OVERLOAD AND OXIDATIVE STRESS IN CHRONIC KIDNEY DISEASE

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DISCLOSURE OF INTERESTS

received commercial/research assistance, speaker's fees and financial sponsorship to attend conferences, advisory boards and clinical trials from Amgen, Janssen Cilag, Pfizer, Roche, sanofi-Aventis, Sandoz and Vifor Pharma.....





	China	Australia
Population	1.357 billion (2013)	22,6 million
Area (km²)	9.597,000	7,617,930
Dialysis/Tx (n)	300,000 (2012)/?	10,532/7600
Nephrologists: Number/ave age	8000 (2008)	175/48

GOSFORD HOSPITAL





What Are The Concerns With Iron?





KDIGO 2014 Controversies Conference
San Francisco

IRON MANAGEMENT IN CHRONIC KIDNEY DISEASE

Areas to be covered:

1. Iron deficiency verses iron overload
2. Oxidative stress

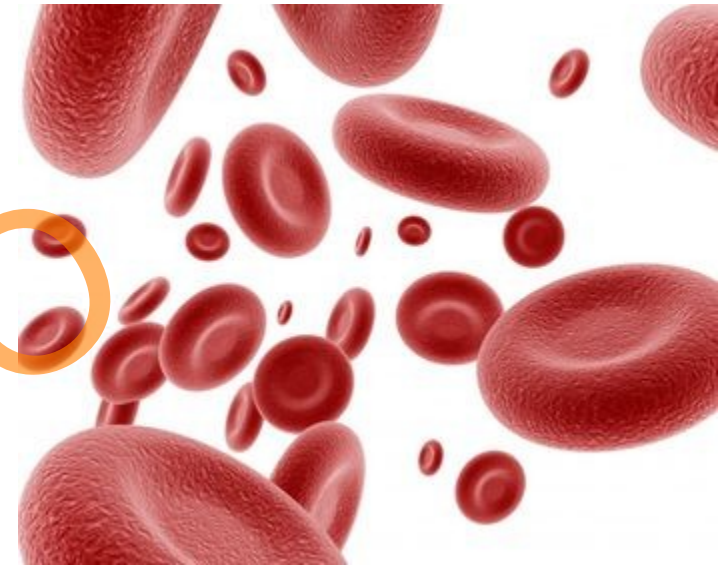
3. Risk of infections
4. Hypersensitivity to iron

How many red blood cells are made per minute?

- 2,000,000
- 120,000,000
- 173,000,000,000
- 63,072,000,000,000
- 4,415,040,000,000,000

Red Blood Cell Production

- 2,000,000 cells/second
- 120,000,000 cells/minute
- 173,000,000,000 cells/day
- 63,072,000,000,000 cells/year
- 4,415,040,000,000,000 cells/70 years



MANAGEMENT OF UREMIC ANEMIA: WHAT ARE THE ESSENTIAL INGREDIENTS?

Iron



EPO

POPEYE





Spinach Iron and Popeye Myth

Google Search

I'm Feeling Lucky

How much iron is in spinach?

- Not very much: 2.7 mg/100g, 21% of daily intake, but high in oxalate, inhibiting absorption
- Popeye: cartoon character, spinach had a lot of vitamin A
- Reasons:
 - German scientist put decimal point in the wrong place
 - Measured dried not fresh spinach, iron pot contamination
- BMJ Christmas article: Popeye would have better eating the actual cans

Hamblin BMJ 1981; 283: 1671-4

PART 1:

IRON DEFICIENCY VS. OVERLOAD



Causes of Absolute Iron Deficiency

- Blood losses associated with:^{1–3}
 - Laboratory tests and hospitalization
 - HD (from dialyzer and access)

	Healthy Patient	Non-dialysis CKD Patient	Hemodialysis Patient
Daily Blood Loss	0.83 ml/d	3.2 ml/d	5.0 ml/d
Annual Blood Loss	0.3 L/yr	1.2 L/yr	2–5 L/yr
Annual Iron Loss	0.1 g/yr	0.4 g/yr	1–5 g/yr

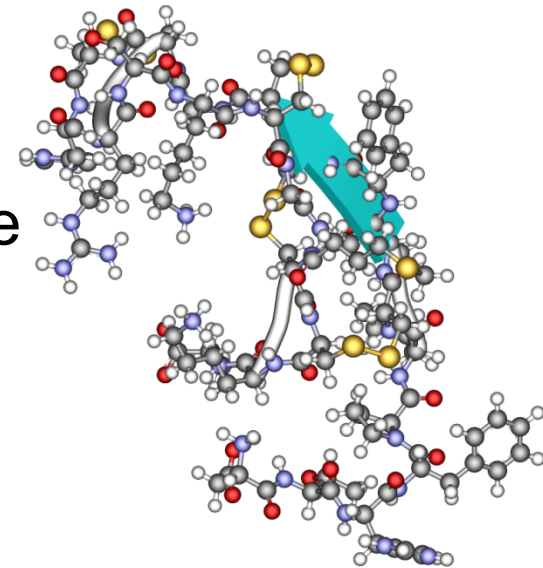
1. Sargent JA et al. Blood Purif 2004;22:112-113.
2. Rosenblatt SG et al. Am J Kidney Dis 1982;1:232-236.
3. Wizemann V et al. Kidney Int Suppl 1983;16:S218-S220.

Causes of Absolute Iron Deficiency

- GI losses due to anticoagulant or antiplatelet drugs.
- Reduced iron absorption due to medications (e.g., proton pump inhibitors and phosphate binders).
- Reduced iron absorption due to increased hepcidin levels.
- Reduced iron intake due to poor appetite, diet, and malnutrition.

Causes of Functional Iron Deficiency

- Inflammation results in:
 - Sequestration of iron within reticuloendothelial system (RES).
 - Reduced total iron binding capacity.
 - Lowered absolute amount iron available for erythropoiesis
 - Mediated by elevated hepcidin.
- ESAs can create increased demand for iron and worsen iron availability in chronically inflamed patients.



Measuring Iron Deficiency

- Both ferritin and TSAT have shortcomings when used to assess iron status.
- Ferritin 200 $\mu\text{g/L}$ is frequently used as a cutoff value in dialysis patients.
- Although evidence is limited, TSAT $<20\%$ generally indicates absolute iron deficiency.¹ However, TSAT $>20\%$ does not exclude this condition.
- *In CKD patients, ferritin and TSAT should be used together.*^{1,2}
- Percentage of hypochromic red cells and reticulocyte Hb content can indicate inadequate iron supply, but the method is not practical for wide adoption.

1. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int Suppl.* 2012;2:279–335.
2. NICE Guideline No. 8, 2015.

How much iron is too much?



...and where does it go?

Iron Dosing

- Precise dosing to correct iron deficiency is uncertain, since the true amount of iron loss is unknown.
- In general, IV iron doses >3 g/yr are likely to be associated with an increased risk of exceeding the ongoing iron loss and inducing positive iron balance.
- The consequences of applying IV iron in excess of ongoing losses remain unknown.
- Higher IV iron requirements should prompt investigation of increased losses (especially GIT).

Iron Compartmentalization in the Body

It has been hypothesized that parenchymal iron excess and labile iron can be harmful while iron sequestered within cells of the reticuloendothelial system may be of less concern

Defining Iron Overload

- No feasible method exists to determine total body iron content.
- Iron overload is a condition of increased body iron content.
 - Possibly associated with risk of organ dysfunction
- Pathologic iron overload is a condition of increased total body iron content with signs of organ dysfunction.
 - Described for hematological diseases (e.g., hemochromatosis)

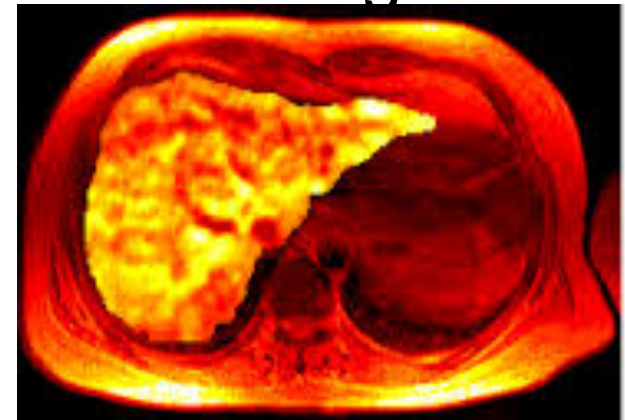
Assessing Iron Overload

- Elevated serum ferritin does not always correlate with elevated liver iron content.
- High ferritin + high TSAT can be of particular concern based on observations in hereditary hemochromatosis and transfusion-induced iron overload.



MRI: Assessing Iron Overload

- MRI has been shown to be reliable for detecting tissue iron content in the non-CKD population.
- However, there is limited experience in HD patients.
- The relevance of increased liver iron content in the absence of elevated liver enzymes is unclear.
- There is insufficient evidence to use MRI to guide IV iron therapy.



Organ Toxicity Induced by Iron Overload

- The magnitude, distribution, and duration of iron overload in CKD may be insufficient to produce similar toxicity as observed for hematological disorders.
- Given that IV iron use has increased markedly in HD over the last few years, the exposure may not have been long enough to detect toxicity.
- End-organ damage has not been established unequivocally; therefore, the toxicity of repeated high-dose IV iron cannot be excluded.

Case Study: Huang Fu

- 58-y.o.male on HD for 3 yrs
- End-stage kidney failure due to hypertensive nephropathy
- Known chronic liver disease due to hepatitis C
- On EPO alfa 4000 units x3 per week + IV iron 200 mg monthly
- Lab results
 - Hb 9.4 g/dL
 - Ferritin 1145 µg/L
 - TSAT 18%
 - CRP 2 mg/L



Case Study: Huang Fu

What would you do next?

- A. Continue present dose of EPO and IV iron
- B. Increase his dose of EPO and continue IV iron
- C. Increase his monthly prescription of IV iron and continue same dose of EPO
- D. Increase both his dose of EPO and his monthly dose of IV iron
- E. Continue EPO and reduce monthly iron dose

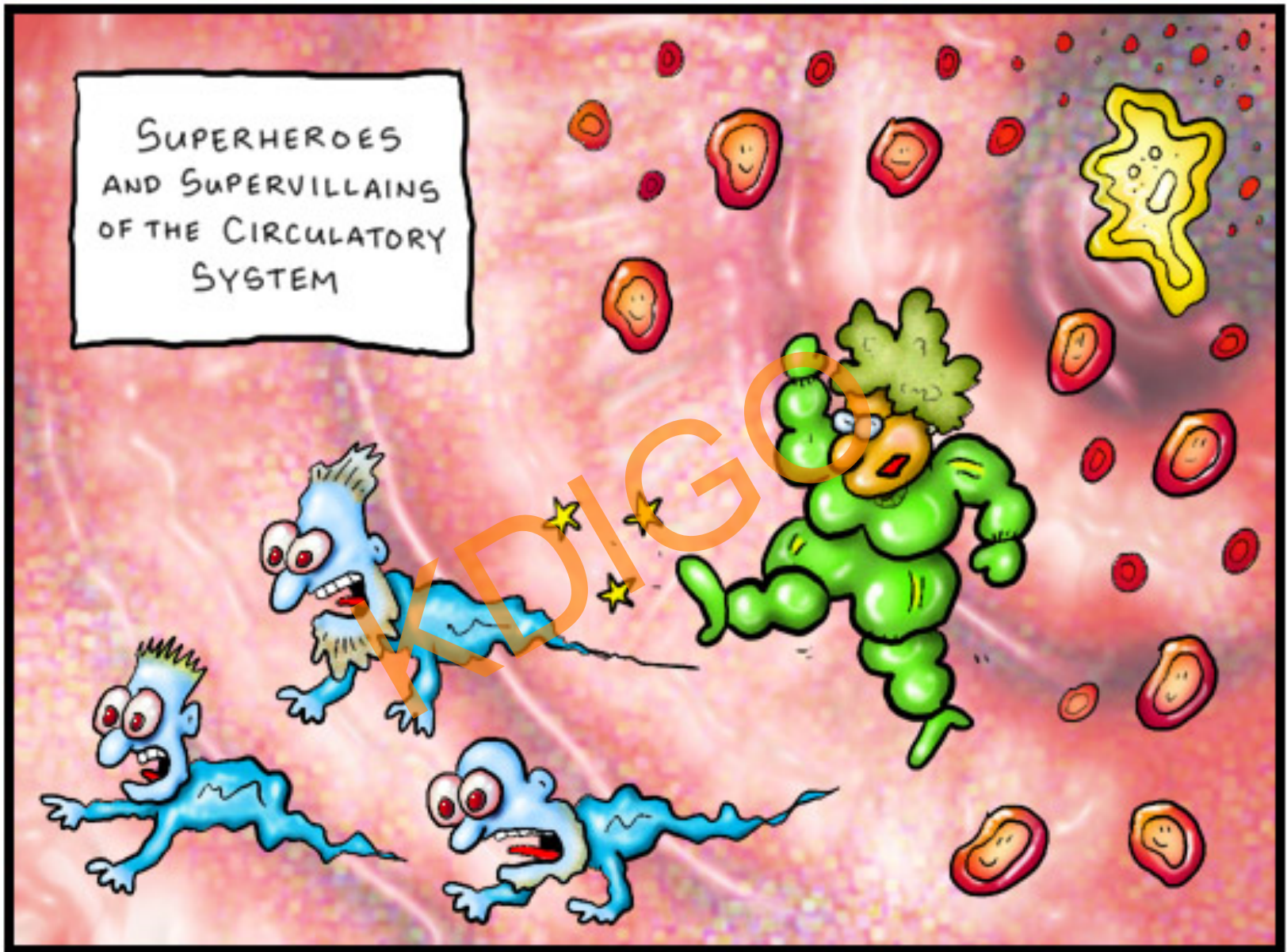
PART 2:

OXIDATIVE STRESS

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SUPERHEROES
AND SUPERVILLAINS
OF THE CIRCULATORY
SYSTEM



Auntie Oxidant kicks out the Free Radicals.

Oxidative Stress in CKD

- Oxidative stress early in CKD and is thought to herald poor prognosis.
- Overproduction of reactive oxygen/nitrogen species or impairment in the cellular antioxidant enzymatic activities, leading to oxidation of macromolecules.
- Markers (NO_2 , HOCl, and OH) are present in uremic plasma and are thought to be the fingerprints of increased oxidative stress.
- However, diagnostic tools and the relevance of these markers to guide therapy in CKD are not established.

IV Iron, Oxidative Stress, and CV Risk

- IV iron promotes oxidative damage of peripheral lymphocyte DNA¹ and endothelial dysfunction.^{2,3}
- However, the question of how IV iron accelerates atherosclerosis remains unresolved.
- Accumulation of iron in plaques has not been proven to promote CV disease.
- Limitations of observational studies do not allow any firm conclusions to be made on IV iron dose and CV risk.

1. Kuo KL et al. J Am Soc Nephrol. 2008;19:1817-1826.
2. Kamanna VS et al. Am J Nephrol. 2012;35:114-119.
3. Rooyackers TM et al. Eur J Clin Invest. 2002;32 (Suppl 1): 9-16.

Case Study: Meiying

- 68-y.o. female on HD for 6 yrs
- On EPO and IV iron to maintain ferritin levels above KDIGO minimum
- Wants to stop IV iron because of his concerns about “oxidative stress”



Case Study: Ha-joon

What would you do next?

- A. Agree to Meiyong request and stop IV iron without further discussion
- B. Tell Meiyong you will run some tests to assess oxidative stress level
- C. Continue with IV iron after explaining the reasons for confusion in the medical literature
- D. Do options B and C

Areas to be covered:

1. Iron deficiency verses iron overload
2. Oxidative stress

3. Risk of infections
4. Hypersensitivity to iron



David C Wheeler

- **David's current positions include Professor of Kidney Medicine at University College London, UK and Honorary Consultant Nephrologist at the Royal Free London NHS Foundation Trust.**
- **He is Clinical Lead for Division 2 of the North Thames Clinical Research Network and heads a team of eight clinical trials nurses/practitioners at the Centre for Nephrology, Royal Free Hospital in London. He has been involved in clinical practice guideline development for several organisations, most recently for KDIGO, of which he is currently Co-Chair.**

PART 3:

RISK OF INFECTIONS

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IV Iron: Infection Risk in HD Patients

- Critical review¹ of studies (largely observational) evaluating infection risk association with a) ferritin, and b) iron usage:
 - Ferritin: 9 studies showed association (1.5- to to 3.1-fold higher incidence of infection or infection-related mortality), 4 studies did not.
 - Iron usage: 12 studies showed association (14%–45% higher risk of infection-related mortality), 10 did not.

1. Ishida JH, Johansen KL. Semin Dial. 2014;27:26–36.

IV Iron: Infection Risk in HD Patients

- Bolus dosing was reported to show higher risk than maintenance dosing for patients with a catheter and history of infection.¹
 - In contrast, maintenance dosing or low dosing was not associated with increased risk.



1. Brookhart MA, et al. J Am Soc Nephrol. 2013;24:1151–

IV Iron in HD: Infection-Related Outcomes

Relationship between IV iron dose and infection-related hospitalization.¹

Duration of Iron Exposure	Doses (mg)	N (Hosp.)	Infectious Hosp: HR (95% CI)
1 month	None	2187	0.92 (0.76, 1.11)
	>0 to 150	1200	1 (ref)
	>150 to 350	1648	0.94 (0.77, 1.15)
	>350	1825	0.91 (0.77, 1.09)
3 months	None	1047	1.03 (0.81, 1.33)
	>0 to 450	1381	1 (ref)
	>450 to 1050	2151	1.01 (0.81, 1.25)
	>1050	1513	1.08 (0.86, 1.36)
6 months	None	399	1.15 (0.79, 1.68)
	>0 to 900	1383	1 (ref)
	>900 to 2100	2589	0.94 (0.75, 1.19)
	>2100	845	1.26 (0.94, 1.69)

1. Tangri N, et al. Nephrol Dial Transplant. 2015;30:667–675.

DEcIDE-ESRD 9544 HD patients

Studies in PD and Nondialysis Patients

- One study showed more peritonitis episodes in PD patients after IV iron infusion.¹
- A recent single-center RCT (REVOKE) also showed IV iron was associated with higher rate of adverse events; however, the findings are controversial.²
- The FIND-CKD global multicenter study (non-dialysis CKD patients) found that the incidence of infections and CV events was identical for high-ferritin, low-ferritin, and oral iron groups.³

1. Prakash S, et al. *Perit Dial Int.* 2001;21:290–295.

2. Agarwal R, et al. *Kidney Int.* 2015;88:905–914.

3. Roger SD et al. *Nephrol Dial Transplant* . 2016 on line

REVOKE Study

	REVOKE ¹	
	Oral ferrous sulfate	IV iron sucrose
Patients	69	67
Study Period	104 weeks	
SAE (%)	40 (58)	37 (55)
SAE infections (%)	11 (16)	19 (28)

1. Agarwal R, et al. *Kidney Int.* 2015;88:905–914.

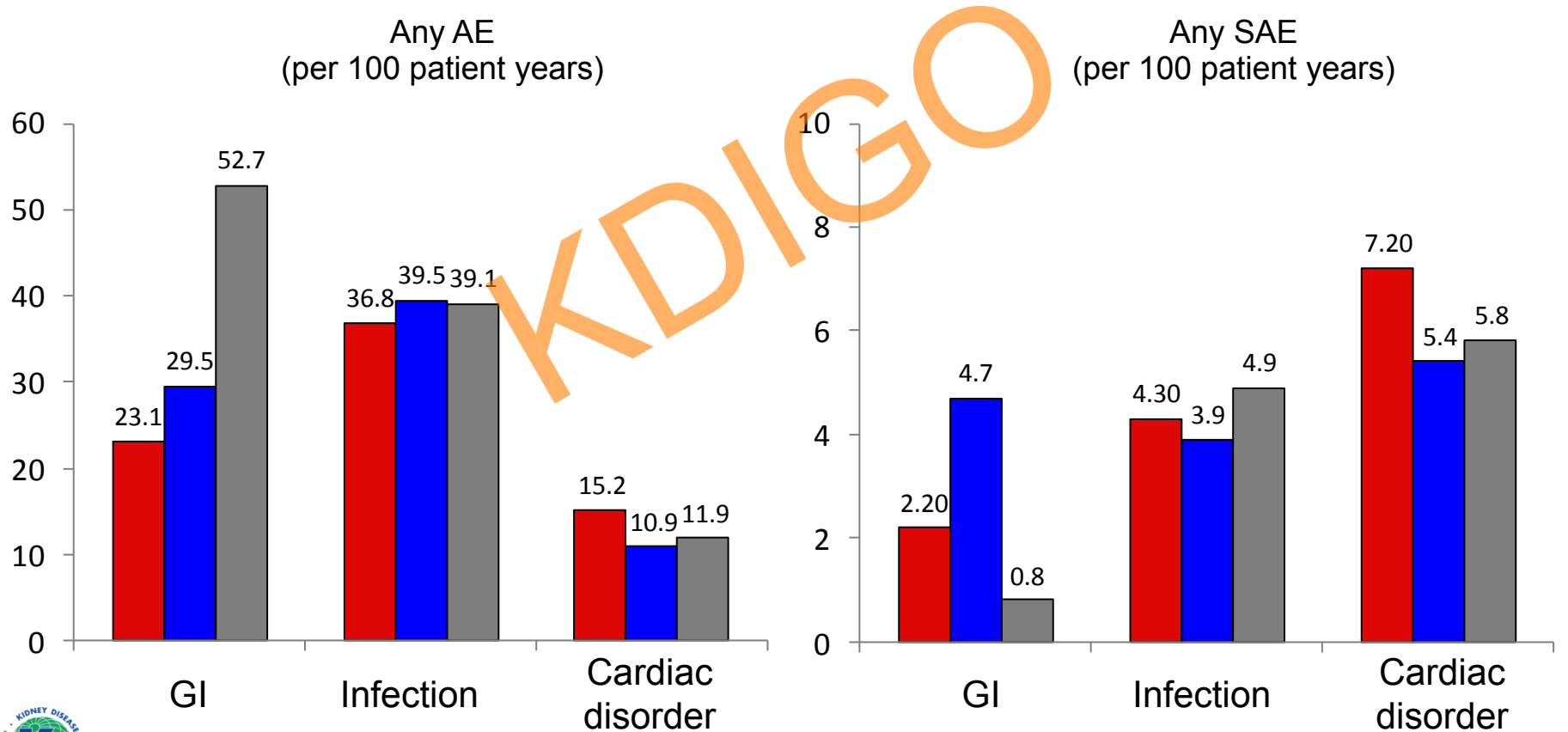
FIND-CKD Study

	FIND-CKD ¹	
	Oral ferrous sulfate	IV ferric carboxymaltose
Patients	312	304
Study Period	56 weeks	
SAE (%)	59 (19)	75 (25)
SAE infections (%)	12 (3.8)	11 (3.6)

1. Macdougall IC, et al. Nephrol Dial Transplant. 2014;29:2075–2084.

FIND-CKD AEs & SAEs of interest

High ferritin FCM Low ferritin FCM Oral iron



Existing Evidence: Inconclusive

- Studies in HD, PD, and non-dialysis CKD patients provide conflicting evidence for the association between IV iron and infection risk.
 - Most data are derived from observational studies in HD (subject to confounding) and the few RCTs conducted to date were of short duration or underpowered to assess the risk of infection
- Current KDIGO recommendations are still prudent which calls for:
 - balancing potential benefits vs. risks of IV iron
 - avoiding IV iron use in patients with active systemic infections

Case Study: Wang Fang

- 67-y.o. female on HD
- Admitted with ruptured diverticular abscess and cutaneous fistula
- On weekly protocol: iron sucrose 100 mg/wk (KDOQI Guidelines) and epoetin alfa 6000 units/wk, target Hb 10.0–11.5 g/dL
- Lab results
 - Hb 9.2 g/dL
 - Ferritin 335 $\mu\text{g/L}$
 - TSAT 10%



Case Study: Wang Fang

What would you do next?

- A. Increase the EPO dose
- B. Continue to administer IV iron due to low TSAT
- C. Withhold IV iron and increase EPO dose
- D. Withhold IV iron and maintain EPO dose
- E. Continue with the same dose of EPO and frequency of IV iron

PART 4:

HYPERSENSITIVITY TO IRON

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Hypersensitivity Reactions to IV Iron

- Concerns regarding IV iron safety largely originate from older formulations containing dextran.
 - Higher-molecular weight (HMW) iron dextran should not be used, since alternative formulations are available.
 - Alternatives include LMW iron dextran, iron sucrose, ferric sodium gluconate, ferric carboxymaltose, iron isomaltoside 1000, ferumoxytol.
- These formulations may be viable alternatives to oral iron and may be cost-effective in certain settings, despite higher cost.

Severe Hypersensitivity Reactions

- Excluding HMW iron dextran, anaphylactic reactions to IV iron are extremely rare, with an incidence of <1:200,000.
- No anaphylactic reactions have been demonstrated with intradialytic iron or newer oral iron formulations, but risks cannot be ruled out.
- No established and validated tests exist to predict or confirm iron hypersensitivity.

Possible Risk Factors for Hypersensitivity

- No established and validated tests exist to predict or confirm iron hypersensitivity.
- The following patient characteristics may indicate a higher risk for hypersensitivity reactions.

- Prior reaction to any IV iron formulation
- Moderate to severe asthma
- Multiple pre-existing drug hypersensitivities or allergies
- Pre-existing immune-mediated disease (e.g., autoimmune disorders)
- Mast cell-associated disorders
- High TSAT or low plasma transferrin levels, which may increase the likelihood of circulating labile iron during infusion

Local skin reactions to extravasated iron can occur. Infusion-specific risk factors such as use of higher doses and rapid rate of infusion should also be considered when evaluating for any potential reactions. Whether generic formulations have a greater propensity for increased labile iron reactions is as yet unclear.

Minor Reactions

- Minor reactions to IV iron include flushing, mild chest discomfort, dizziness, light-headedness, nausea, or itching.
- These reactions resolve when the infusion is stopped or slowed and should generally not preclude ongoing IV iron therapy.

WHAT NOW IN



Research Recommendations: Summary

- Development of a methodology to objectively determine body iron stores and tissue distribution in CKD patients.
- Do thresholds for increased risk of organ damage in patients with HFE hereditary hemochromatosis apply to CKD patients?
- Further clarification of the predictive value of hepcidin.



Research Recommendations: Summary

- Further studies to assess the safety and efficacy of IV iron using hard clinical endpoints.
- Observational studies of risks/benefits of IV iron in predialysis, PD, and transplant patients.
- Development of a standardized questionnaire to report any adverse reaction associated with IV iron.



Conclusions

- Available data do not allow any firm statement to be made on the potential dangers of high-dose iron use and high ferritin levels.
- RCTs are needed to assess the safety and efficacy of IV iron therapy using hard clinical endpoints.
 - The ongoing, event-driven trial, PIVOTAL, recruiting > 2000 HD patients across 50 sites in UK, randomized to a high and low IV iron regimen (planned follow-up of 2-4 years) will help to fill this gap of evidence.

PIVOTAL

Proactive IV iron Therapy in haemodialysis patients

KDIGO Clinical Practice Conference | August 25-26, 2016 | Nanjing, China



Conclusions

- There is consensus that further studies are needed to determine the clinical relevance of iron therapy beyond stimulation of erythropoiesis in CKD such as in patients with congestive heart failure, pulmonary arterial hypertension, restless leg syndrome and premenopausal women with low ferritin.
- Meanwhile, nephrologists would do well to recognize the benefits and limitations of IV iron therapy.

So what is the right path in iron management?

