

Intravenous iron: efficacy & safety

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Iron repletion

The choice

- Oral vs intravenous
- Intramuscular *not* recommended
 - Tattooing
 - Nerve injury
 - Sarcoma risk
 - Medical Defence Org. discourage its use
- Blood transfusion – for circulatory support not iron deficiency

Intramuscular iron



Current guidelines on iron repletion

- *Oral supplementation* is regimen of choice
- *Parenteral iron* should be used “when there is an intolerance to at least two oral preparations, or non-compliance”

*BSG Guidelines: Goddard et al Gut
2000*

Any relevant textbook

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Based upon:

- Oral iron is cheap & safe
- Iron malabsorption is very uncommon
- Oral iron nearly always successful
- Oral = IV iron in rapidity of ↑Hb
- IV iron is dangerous

Oral or intravenous iron

Issues to consider

- Price
- Efficacy
- Speed of repletion
- Safety

1. Price

- Oral cheap – but may need 3 months' Rx
- IV – relatively expensive, particularly if delivered as in-patient
 - Drug
 - Bed/disposables charge

2. Efficacy

- **Compliance**
 - Expect poor compliance with oral iron (<75%)
 - Compliance 'guaranteed' with IV
- **Will oral iron be absorbed?**
 - Intestinal iron absorption impaired:
 - Systemic inflammation
 - Untreated coeliac disease
 - Post-gastrectomy (partial/total)

Functional iron deficiency

- Systemic cytokines ⇒ ↑ hepcidin
 - ⇒ ↓↓ intestinal absorption
 - ⇒ ↓↓ release from stored iron

Functional iron deficiency

- Systemic cytokines \Rightarrow \uparrow hepcidin
 - \Rightarrow $\downarrow\downarrow$ intestinal absorption
 - \Rightarrow $\downarrow\downarrow$ release from stored iron



\downarrow Transferrin saturation

Chronic \Rightarrow \downarrow iron stores

Functional iron deficiency

Therapeutic implications

- If there is a systemic inflammatory response, it can be assumed that oral iron will not be absorbed
- Serum ferritin will not be useful in the decision regarding the use of iron supplementation
 - Iron stores are not the issue
 - Ferritin is an acute phase protein

Evidence base for iron repletion

Short-term benefits and risks of intravenous iron: a systematic review and meta-analysis

Éric Notebaert, Jean-Marc Chauny, Martin Albert, Simon Fortier, Nancy Leblanc, and David R. Williamson

TRANSFUSION 2007;47:1905-1918.

- 13 evaluable RCTs
- Heterogeneity & poor reporting of AEs
- Comparator = oral Fe or no Fe
- Conclusions
 - Evidence base is awful
 - Analysis unhelpful

Oral vs IV iron

Comparative studies

- **Chronic kidney disease**
 - Efficacy: IV > oral; IV works when oral fails
- **Obstetrics**
 - IV \geq oral in \uparrow Hb, repleting stores, tolerance
- **Inflammatory bowel disease**
 - IV Fe > oral Fe + EPO (by 2 fold)
- **Autologous blood transfusion**
 - IV > oral – no, units donated; with EPO

Intravenous Ferric Carboxymaltose Compared With Oral Iron in the Treatment of Postpartum Anemia

A Randomized Controlled Trial

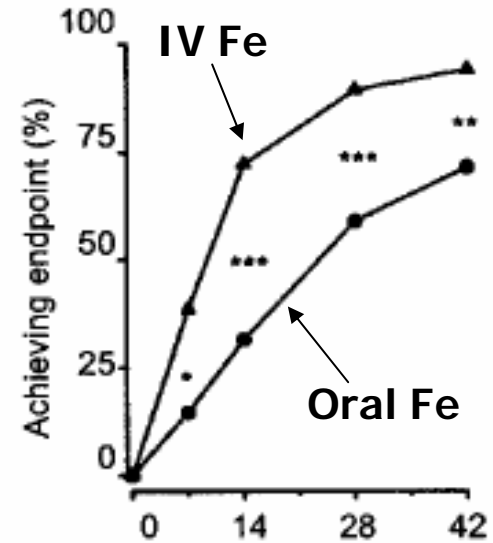
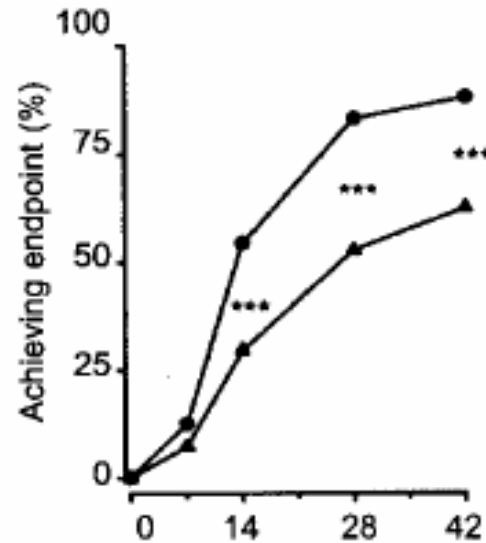
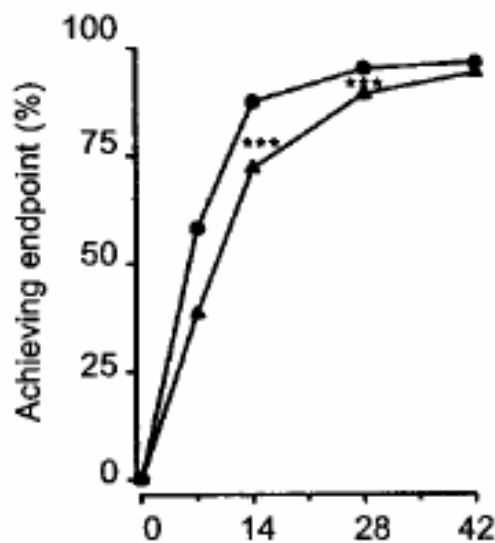
Obs Gynecol 2007

David B. Van Wyck, MD, Mark G. Martens, MD, Melvin H. Seid, MD, Jeffrey B. Baker, MD, and Antoinette Mangione, MD, PharmD

↑Hb >20 g/l

↑Hb >30 g/l

Hb >120 g/l



n = 352

Time after initiating treatment (days)

Intravenous Ferric Carboxymaltose Compared With Oral Iron in the Treatment

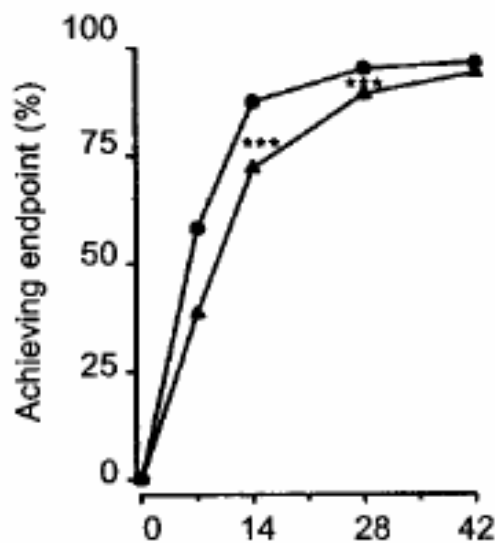
Compliance

- IV Fe = 98% (95%CI: 96-100)
- Oral Fe = 84% (95%CI: 80-88)

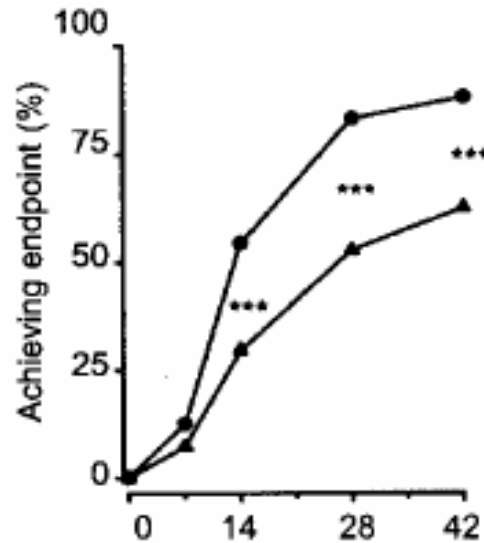
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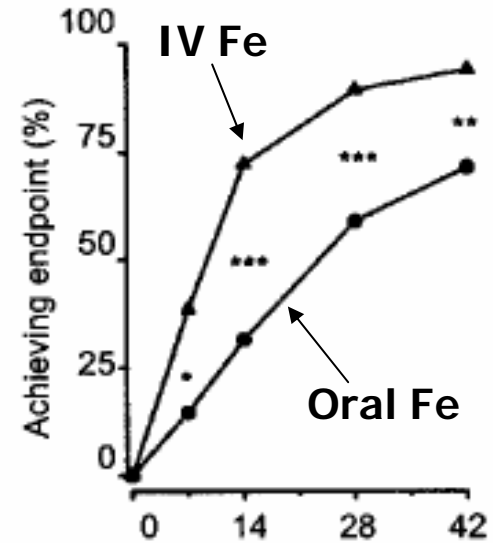
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A



B

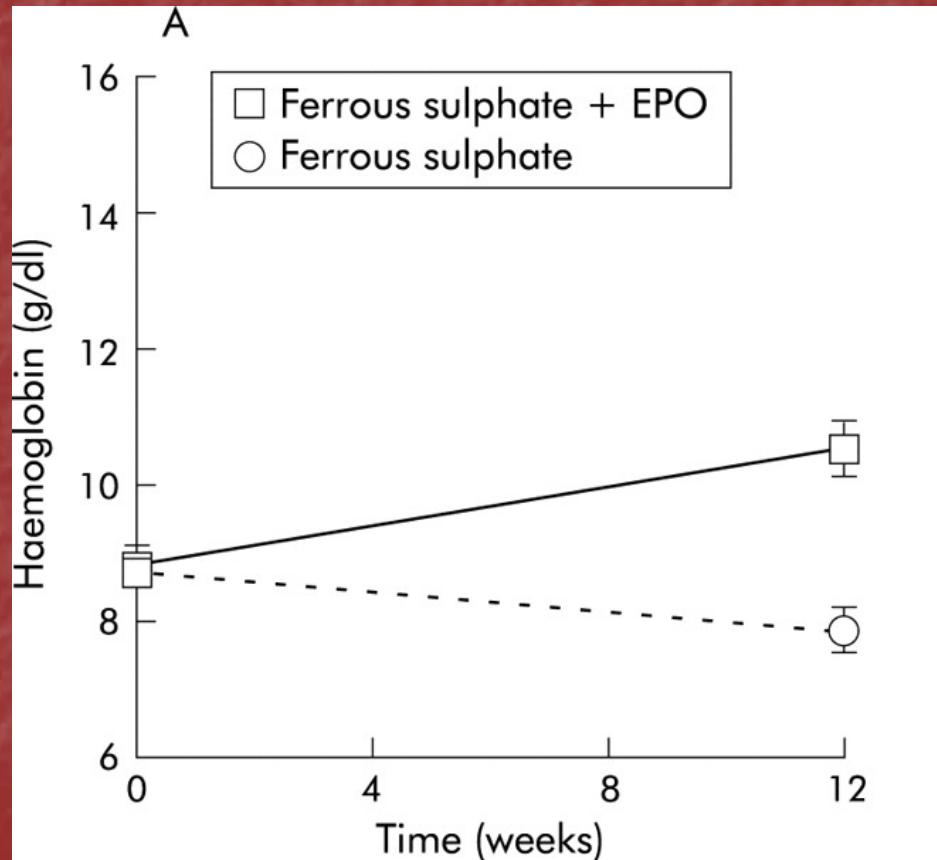


C

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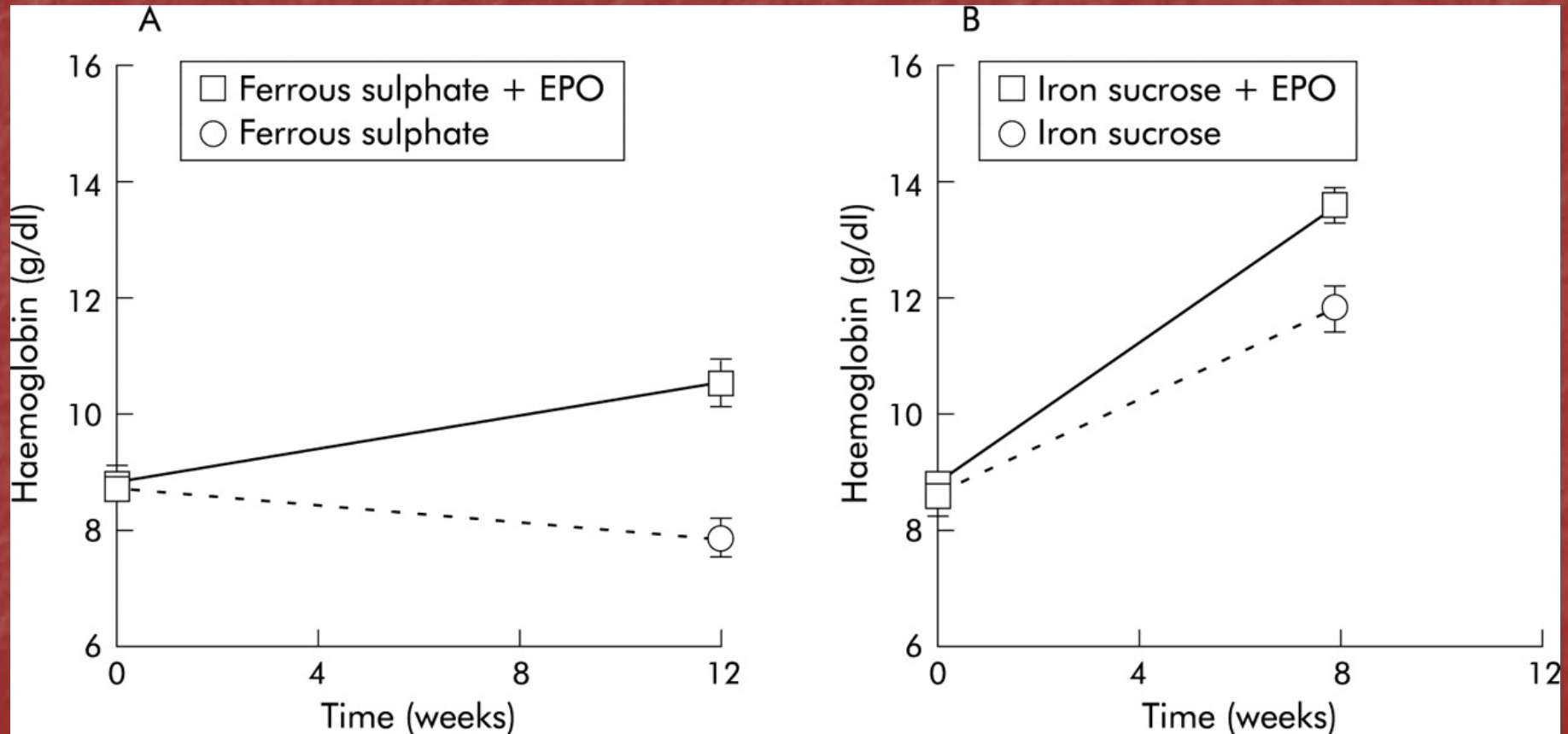
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Oral vs IV iron replacement therapy in IBD



Gasche, C et al. Gut 2004;53:1190-1197

Oral vs IV iron replacement therapy in IBD



4. Speed of repletion

If intestinal absorption is normal, will IV Fe lead to faster rise in Hb than oral Fe?

- Results variable
 - Oral Fe not reported to be faster than IV Fe
 - Oral Fe = IV Fe
 - Oral Fe < IV Fe

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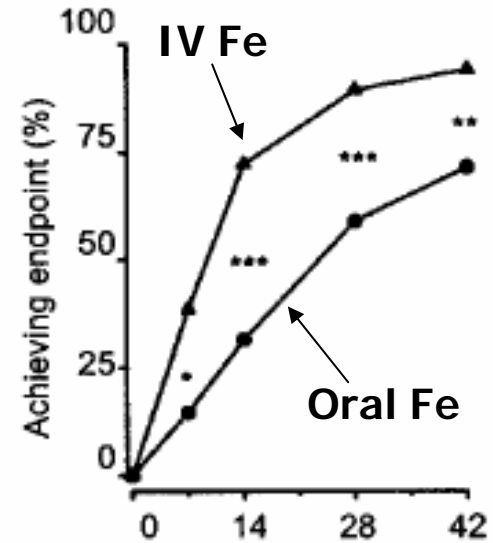
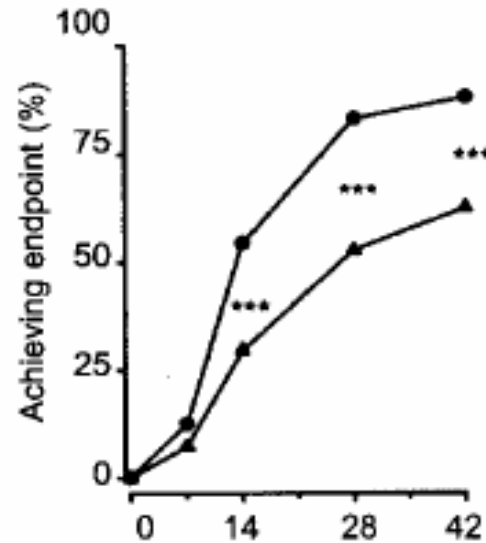
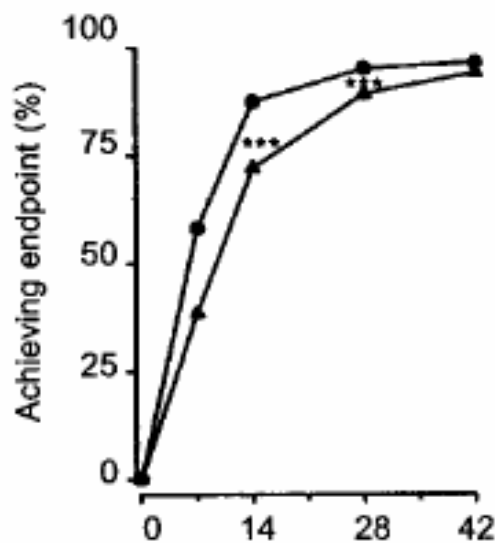
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5. Safety

Theoretical basis for iron-related AEs

- Oxidative stress \Rightarrow *worsen inflammation*
 - $\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{OH}^\cdot + \text{OH}^- + \text{Fe}^{3+}$ (Fenton reaction)
- Promote growth and survival of ferrophilic bacteria \Rightarrow *infection*
- Iron toxicity
 - Free iron overloading transferrin (IV)
 - Chronic administration \Rightarrow cardiac toxicity (IV)

5. Safety

Oral iron

- Side effects – up to 40% - mainly GI
- Dangers
 - Exacerbate intestinal inflammation
 - Localised GI ulceration if stenosis or motility problem
 - Black faeces
 - misinterpretation
 - precludes colonoscopy

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Table 2. Adverse Reactions by More Than 2% of Patients (Safety Population) in Either Treatment Group, by Classification, Considered to Be Drug-Related by Investigator

Adverse Event Classification	IV Ferric Carboxymaltose (n=174)	Oral Ferrous Sulfate (n=178)	<i>P</i>
All GI disorders	11 (6.3)	43 (24.2)	<.001
Constipation	6 (3.4)	20 (11.2)	.007
Diarrhea	0 (0.0)	7 (3.9)	.015
Nausea	2 (1.1)	13 (7.3)	.006
Pruritus, rash, or both	9 (5.2)	4 (2.2)	.164
Serum transaminase elevation	1 (0.6)	5 (2.8)	.215
Headache	10 (5.7)	5 (2.8)	.196

IV, intravenous; GI, gastrointestinal.
Data are n (%).

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Intravenous iron

- **Available preparations in Australia**
 - **Iron polymaltose** (Ferrum H, Ferrosig)
 - TDI (total dose infusion)
 - Virtually no published data on safety IV
 - **Iron sucrose** (Venofer)
 - 100-300 mg IV no > twice weekly
 - Large body of data esp. from European experience
 - Excellent safety record
 - Anaphylaxis - like hen's teeth
 - TGA approved indication – backstop when iron polymaltose not tolerated in CKD

Iron polymaltose

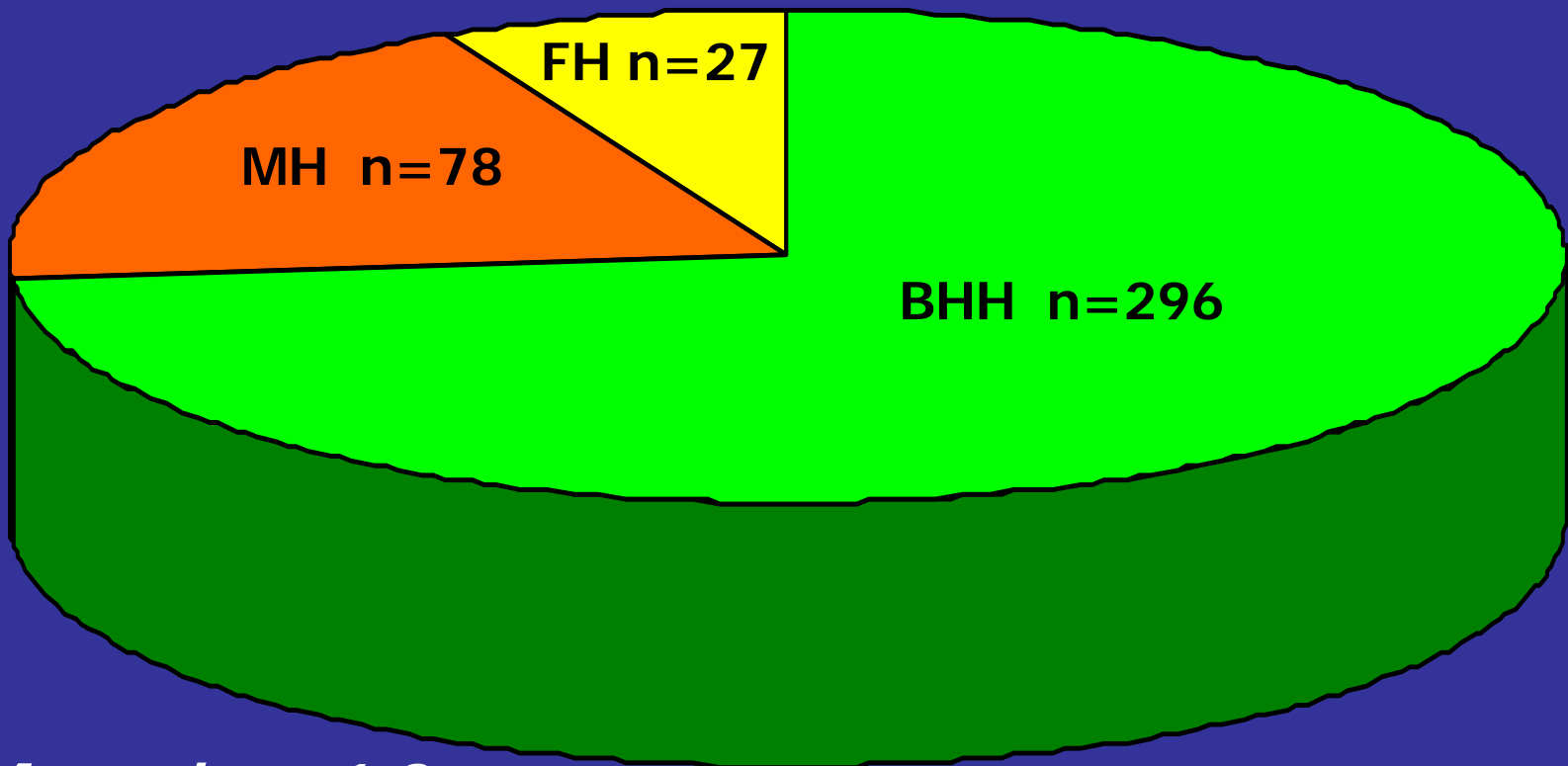
Assumed to carry same risks as iron dextran



- **Infusion protocols**
 - Adrenaline and steroid by the bedside
 - Doctor by the bedside for first 15 minutes
 - 'Test dose' protocol
 - Prolonged infusion (~4 hours)
- **Doctors fearful of its use**

Audit of in-hospital safety of TDI (iron polymaltose)

n = 401 (386 patients) over 2 years



Mean dose 1.3 g

Newnham et al IMJ 2006

Safety

- 384 infusions (96%) uneventful
- Reaction noted in 17 (3.6%)
 - 7 (1.7%) infusions ceased
- No reactions in first 15 minutes
- No cases of anaphylaxis
- 3 infusions with urticaria continued after administration of phenergan and uneventful

Adverse events

REACTION	No.	Infusion ceased
Rash	7	4
Chest pain	3	1
IV Site	3	-
Fever	2	-
Seizure	1	1
Nausea	1	1
TOTAL	17	7

Premedication?

- No premedication in 309 infusions
 - Adverse reaction in 11 (3.6%)
- Premedication given in 92 infusions
 - Phenergan ± hydrocortisone
 - Adverse reaction in 6 (6.5%)

Conclusions

- Well tolerated
- Manageable adverse effects
- No evidence in favour of premedication
- No need for RMO to be in attendance

After the infusion?

- **PI:**
 - adverse events possible but infrequent
- **Aim:**
 - to prospectively evaluate the week after 50 consecutive infusions in Gastroenterology patients

Methods

- Telephone call at day 8
- Adverse reactions classified:
 - Mild – no limitations of daily activity
 - Moderate - limitation of daily activities
 - Severe – confined to bed or medical attention sought

Adverse reactions

- **Infusion-associated**
 - 2 minor
- **After discharge**
 - 32 in 13 patients (26%)
 - 8 severe
 - 10 moderate
 - 14 mild
 - 12 Day 0, 12 Day 1, 6 Day 2
 - Duration 4 (1-8) days

Adverse events

Adverse reaction	n (% reactions)	Severity		
		Mild	Moderate	Severe
headache	10 (31%)	3	4	3
nausea &/or vomiting	7 (22%)	2	3	2
chills and fevers	6 (19%)	2	2	2
arthralgia	4 (13%)	2	1	1
faintness	2 (6%)	2	0	0
rash	2 (6%)	2	0	0
dizziness	1 (3%)	1	0	0
Total	32	14 (44)	10 (31)	8 (25)

Adverse events – previous TDI

<i>Current</i>	AE	No AE
<i>Previous</i>		
AE	1	2
No AE	3	11

Implications

- All transient without sequelae
- Risk not related to dose
- Risk even if no problems before

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- Alternative source of iron if moderate-severe reaction (iron sucrose)
- Should not deter from use of IV route

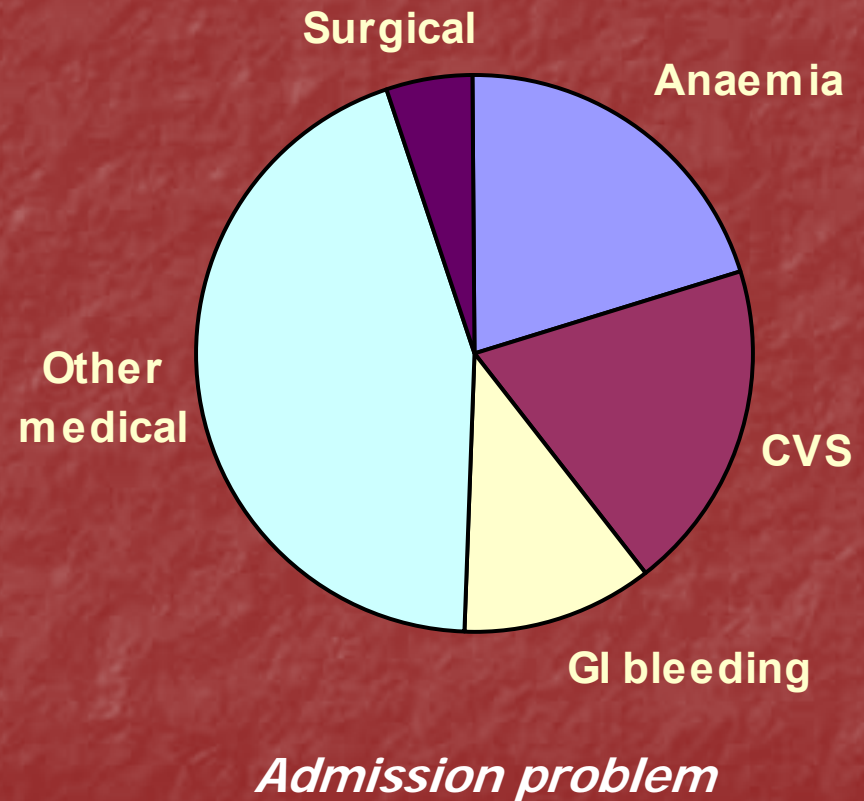
Adverse events – Why?

- Symptoms generally consistent with acute iron toxicity
- Amount of free iron released from iron polymaltose unpredictable
 - quality of the product being used???
 - inherent with iron polymaltose??

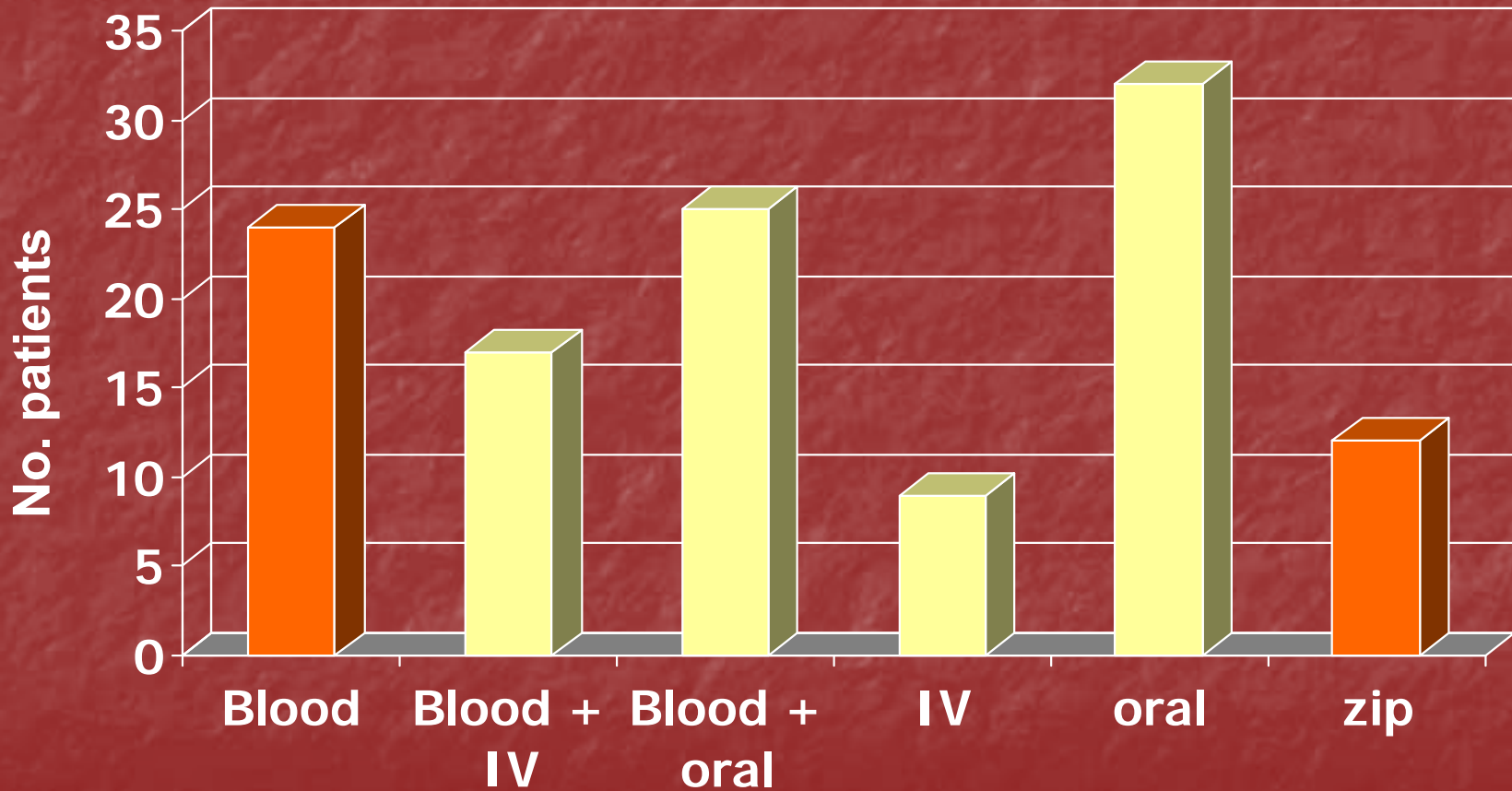
The real world

Audit at a general hospital

- Patients over 2-year period
 - n = 119
 - Median 77 years (range 18-99)
 - 71% women
 - Hb 87 (33-130) g/l

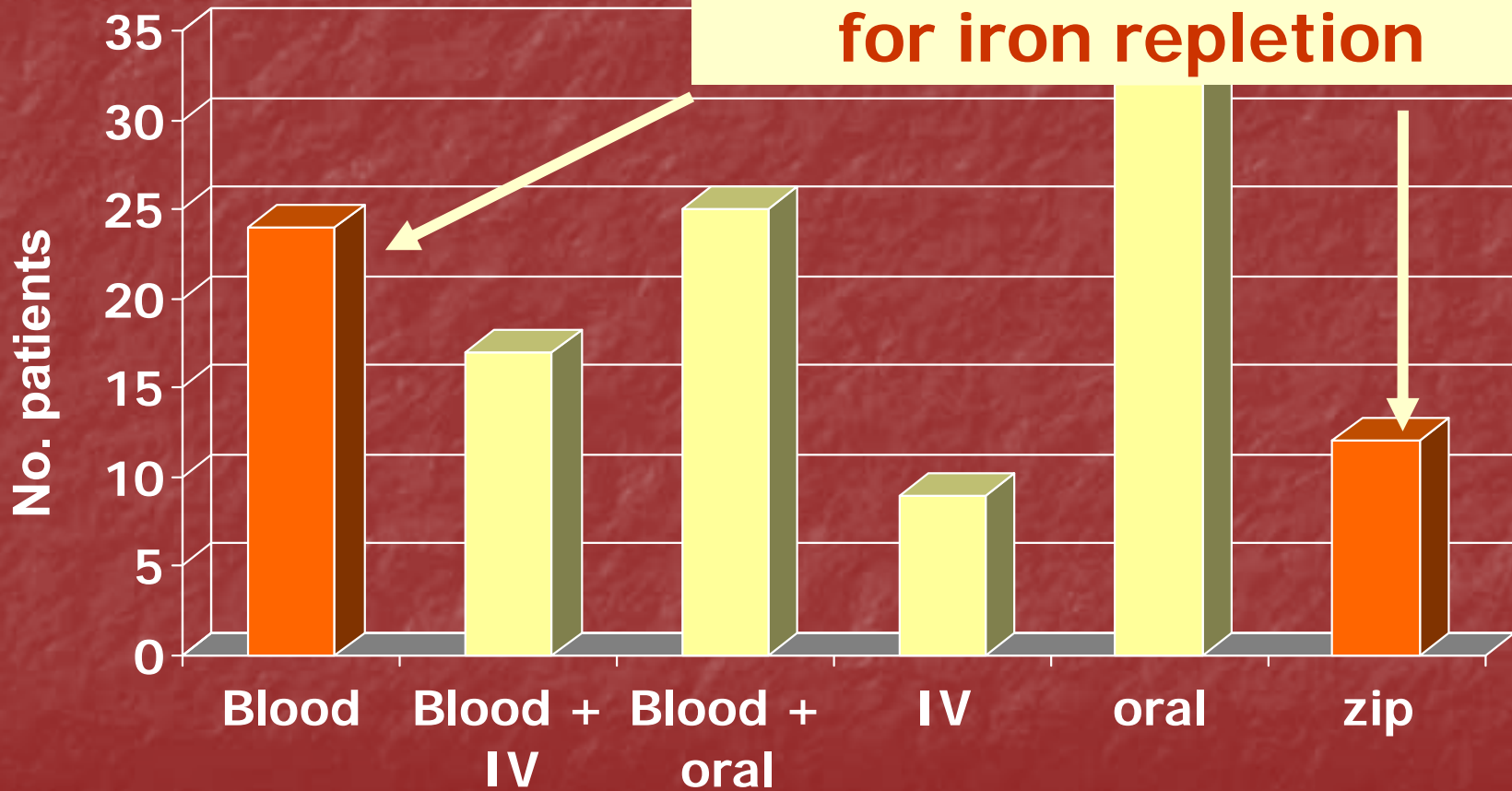


Treatment given (or not)



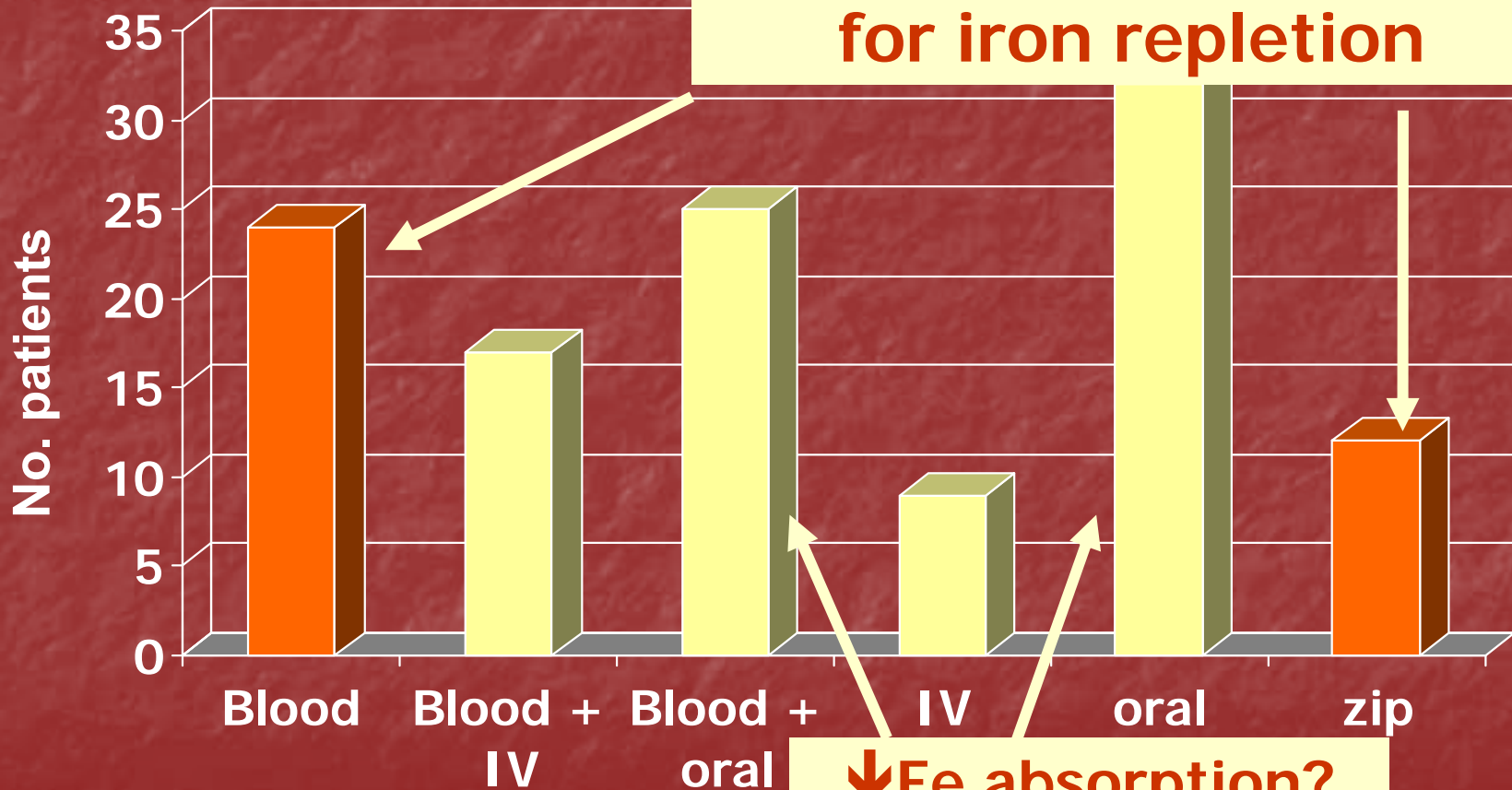
Treatment given (or not)

25% given no strategy for iron repletion



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Ahmad & Gibson IMJ 2006

↓ Fe absorption?
Non-compliant?

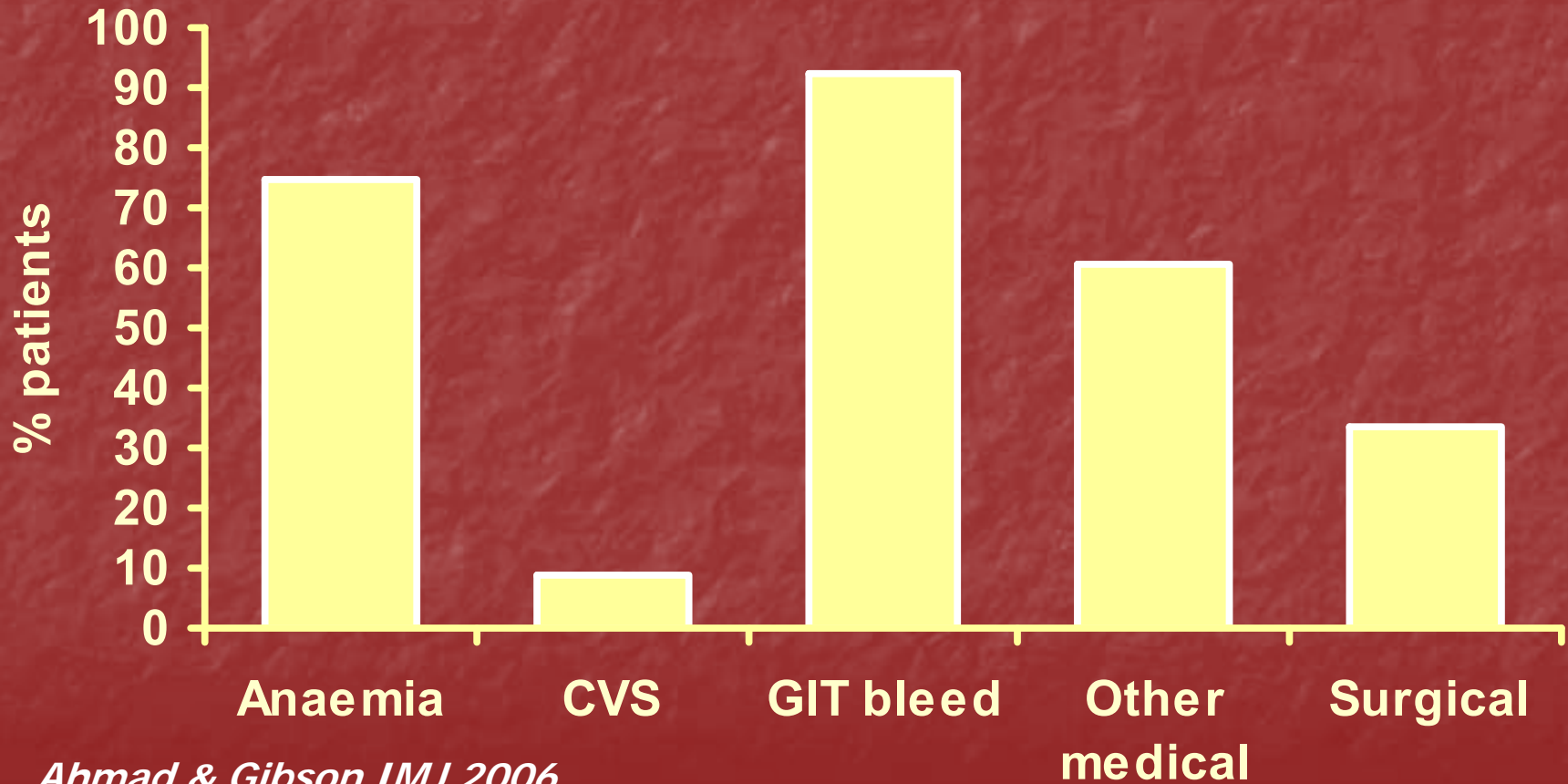
Why?

- Correcting iron deficiency is not a priority
- Poor knowledge base about choices
- No guidelines



Draft guidelines → applied retrospectively

Proportion of patients managed according to guidelines



Ahmad & Gibson IMJ 2006

How to change management approaches

- Education
- Lead by example
- Make it simpler to administer IV iron

IV iron – making it simpler

- Speed of infusion – *faster?*
 - Experience of 90-120 min infusions
- Premedication – *omit?*
 - No benefit demonstrated
- Remove the demand for doctor attendance
 - No value in doctor sitting with patient for first 15 min
- Dose – *proper “total dose”?*
 - 1 g to 3 g = no apparent difference in AEs
- Other administration methods
 - Push IV – 100 mg iron sucrose, iron polymaltose
 - Hospital-in-the-home – iron sucrose

Conclusions

Correcting iron deficiency

■ *Clinical practice*

- Need to be more “iron-aware”
- Need to be more “IV iron-aware”
- Require agreed guidelines and more education

■ *Choice of oral vs intravenous iron*

- Cost – oral iron cheap
- Efficacy – in favour of IV:
 - Gut absorption – cytokine-driven impairment
 - Compliance – poor for oral iron
- Rapidity of effect – IV may be faster
- Safety
 - Oral iron not benign
 - IV well tolerated; adverse effects transient

Stratification by clinical scenario

Scenario	Details	Examples
A. Urgent attention to Hb	Life-threatening anaemia ± ongoing large vol. blood loss	<ul style="list-style-type: none">• <i>Severe anaemia</i>• <i>Anaemia and heart failure</i>• <i>Anaemia and unstable angina</i>• <i>Acute on chronic blood loss</i>

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Blood transfusion + iron infusion

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B. Semi-urgent iron repletion	ID of immediate relevance to disease process or Sx, and its correction likely to improve clinical problem	<ul style="list-style-type: none">• <i>Severe IDA</i>• <i>↑ cardiac workload poorly tolerated (CCF, IHD)</i>• <i>Ongoing loss of iron &/or poor iron absorption</i>• <i>Black stools unwanted</i>• <i>Require surgery ass with potential blood loss</i>

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Iron infusion

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Oral iron or iron infusion (patient preference, efficiency of iron absorption,)		
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