A stain on iron therapy

SUMMARY
Iron staining is an unwanted and in some cases permanent adverse effect of intravenous iron administration. Cosmetically unacceptable staining may cause distress and have psychological implications for the patient.

There should be a suitable indication for parenteral iron therapy. Patients must be advised of the risk of harm and give their informed consent before receiving parenteral iron.

Strategies to minimise the risks of staining with intravenous iron include appropriate cannulation and close monitoring of the infusion. Stop the infusion if there are signs of extravasation.

Laser therapy may be a treatment option in cases of persistent discolouration due to iron staining.

Introduction
Iron deficiency is a common condition and a large contributor to anaemia.1 The prevalence of iron deficiency anaemia is high in younger women and indigenous Australians.2 Treatment options to correct iron deficiency in Australia include oral and parenteral iron.1 Within the last decade the use of intravenous iron has been increasing,4 particularly in the community. This is because of newer iron salts with favourable adverse effect profiles and shorter infusion times for intravenous formulations. These include ferric carboxymaltose and ferric derisomaltose. For patients in hospital, iron polymaltose or iron sucrose can also be used.

An uncommon adverse effect of parenteral iron is skin staining (see Fig.). This is not a new phenomenon as it is a well-known adverse effect of intramuscular iron.5 Iron staining can occur with intravenous infusions if there is extravasation into the surrounding tissue. The use of intramuscular iron administration is limited in practice,3 but the injection can be given into an unexposed site. However, administration at an unexposed site is not necessarily possible when giving iron intravenously. A rise in reports of iron staining6–10 may correspond with the increasing use of intravenous iron in clinical practice.6–13

Incidence of skin staining
The rate of skin discolouration with intravenous iron preparations has been reported in clinical trials as 0.68%14 to 1.3%.15 Postmarketing reports suggest the incidence may be lower and skin necrosis has not been reported. However, iron staining may be under-reported to pharmacovigilance databases. A review of the French pharmacovigilance database from 2000 to 2016 found only 51 cases of cutaneous pigmentation with iron.12 Postmarketing reports to the Therapeutic Goods Administration (TGA) Database of Adverse Event Notifications,16 from March 2014 to October 2019, included 27 cases for ferric carboxymaltose. These reports included the terms skin discolouration or hyperpigmentation, haemosiderin stain, pigmentation disorder, infusion/injection/administration site discolouration, or extravasation. The TGA data include eight cases of pigmentation disorder or skin discolouration with iron polymaltose, with the first report in 2005. There are currently no reports for ferric derisomaltose, but this adverse effect is included in the product information.

Minimising harm
Specific definitive risk factors for extravasation of intravenous iron have not been published. The principles for minimising the harm associated with intravenous iron preparations have been adapted from those applied to intramuscular iron (Box 1).5 They include a good infusion technique (Box 2).
Benign heart murmurs are common in children and are generally not associated with underlying cardiac pathology. When assessing a child with a heart murmur, it is crucial to consider the child’s age, the nature and duration of the murmur, and any accompanying symptoms. A comprehensive physical examination, including auscultation, is essential. Imaging studies such as echocardiography may be indicated to rule out structural heart disease. It is also important to evaluate the child’s overall growth and development and their family history of cardiac conditions. A multidisciplinary approach, involving cardiologists, pediatricians, and other healthcare professionals, is often required to manage and follow these cases effectively.

**Table:**

| Condition | Description |
|-----------|-------------|
| Benign heart murmurs | Common in children, not associated with underlying cardiac pathology |
| Comprehensive physical examination | Auscultation |
| Imaging studies | Echocardiography |
| Overall growth and development | Evaluation |
| Family history | Evaluation |

**Figure:**

- Heart examination
- Echocardiography

**Figure legend:**

- Heart examination
- Echocardiography

**Table notes:**

- Echocardiography is a non-invasive imaging technique used to assess the heart's structure and function.
- It is particularly useful in evaluating the heart’s chambers, valves, and blood flow.
- It can help rule out structural heart disease and is a critical tool in the management of children with heart murmurs.
vital signs in accordance with local protocols for infusions.\textsuperscript{26} Giving intravenous iron infusions overnight must be avoided as it is more difficult to observe extravasation and staining in the dark.

**Staff training**

In order to ensure the best outcomes for patients, health professionals involved with the prescribing, administration and monitoring of intravenous iron must be adequately trained and competent. A set protocol that outlines best practice for intravenous iron administration, including cannulation, should be followed. Staff must be aware of the monitoring requirements and the symptoms of potential adverse effects.

**Management of iron staining**

There are no published guidelines outlining how to manage iron extravasation or skin discolouration following iron infusions. Box 4 gives the best available guidance for acute management to limit the potential for further staining. Clinical photographs should also be taken to capture the extent of the extravasation and to help with monitoring the success of subsequent treatments.

There are limited options to reverse iron staining. Topical therapies, lymphatic drainage and massages have been tried without success.\textsuperscript{9,13} The most evidence for successful reversal of iron staining is with laser therapy.

One review assessed 29 patients who had reported accidental staining from iron infusions over a nine-year period.\textsuperscript{13} Thirteen patients had laser therapy and eight completed treatment. Regression of iron staining took an average of 5.6 laser sessions over one to two years. The type of laser is important with most evidence being for quality-switched Nd:YAG or picosecond. The patient’s individual skin type may also influence the success of laser treatment. In general, laser therapy was well tolerated.

Laser therapy is available in Australia, but there may be significant financial barriers as repeated applications are required. If the patient is concerned about the staining, early referral to a dermatologist with a laser clinic specialising in quality-switched Nd:YAG and picosecond laser is appropriate.

**Review cases to improve patient safety**

When extravasation occurs, prudent review of the patient is warranted. Consider likely contributing factors, such as whether there was a suitable indication for intravenous iron, poor techniques in cannulation, the patient’s own vasculature and any lack of monitoring.

Report these cases to the TGA.

**Conclusion**

There should be a clear indication for using intravenous iron. Patients need to give informed consent for the infusion.

Iron extravasation can be cosmetically unacceptable for patients so strategies should be put in place to prevent it from occurring. These include appropriate vein selection, securing the cannula and close monitoring during the infusion. In addition, the patient should be advised to report any pain, irritation or swelling at the infusion site.

In the event of extravasation and persistent staining, repeated laser sessions over one to two years may be required. However, iron staining can be permanent.

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**Box 3** Clinical features of iron extravasation\textsuperscript{6-13}

| Symptoms during infusion                 |
|------------------------------------------|
| Pain, swelling, feeling of pressure, prickling on the injection site and immediately observable staining. Note: some patients report no pain or other symptoms during the infusion and the discolouration appears hours or days later |

| Extent of skin discolouration             |
|------------------------------------------|
| Can be localised to around the injection site or extend along the length of the arm. May be patchy or consistent discolouration |

| Colour changes                            |
|------------------------------------------|
| Most common – light to dark brown         |
| Less common – black, bluish, purple, grey |

| Symptoms in the longer term               |
|------------------------------------------|
| Generally, discolouration is asymptomatic, but some patients complain of aching, changed sensitivity in the affected area or tenderness on palpation |

| Outcome                                   |
|------------------------------------------|
| In many cases, iron staining is permanent. Some patients report fading of the stain over time or successful treatment with laser therapy |

**Box 4** Acute management of iron extravasation

If the patient complains of pain, swelling, soreness at the injection site or there is any obvious swelling or discolouration, stop the infusion immediately and assess the site

Disconnect the giving set

Aspirate any residual drug from the cannula

Remove the cannula

Apply a cold pack if there is swelling or soreness, however this does not appear to prevent the spread of the stain
Conflict of interest: none declared

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