Prevention and management of acute reactions to intravenous iron in surgical patients

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Abstract

Absolute or functional iron deficiency is the most prevalent cause of anaemia in surgical patients, and its correction is a fundamental strategy within "Patient Blood Management" programmes. Offering perioperative oral iron for treating iron deficiency anaemia is still recommended, but intravenous iron has been demonstrated to be superior in most cases. However, the long-standing prejudice against intravenous iron administration, which is thought to induce anaphylaxis, hypotension and shock, still persists. With currently available intravenous iron formulations, minor infusion reactions are not common. These self-limited reactions are due to labile iron and not hypersensitivity. Aggressively treating infusion reactions with H_1-antihistamines or vasopressors should be avoided. Self-limited hypotension during intravenous iron infusion could be considered to be due to hypersensitivity or vascular reaction to labile iron. Acute hypersensitivity reactions to current intravenous iron formulation are believed to be caused by complement activation-related pseudo-allergy. However, though exceedingly rare (<1:250,000 administrations), they should not be ignored, and intravenous iron should be administered only at facilities where staff is trained to evaluate and manage these reactions. As preventive measures, prior to the infusion, staff should inform all patients about infusion reactions and identify those patients with increased risk of hypersensitivity or contraindications for intravenous iron. Infusion should be started at a low rate for a few minutes. In the event of a reaction, the very first intervention should be the immediate cessation of the infusion, followed by evaluation of severity and treatment. An algorithm to scale the intensity of treatment to the clinical picture and/or response to therapy is presented.

Keywords: intravenous iron, infusion reaction, hypotension, anaphylaxis, management.

Introduction

In major elective surgery, the effects of pre-operative anaemia, blood loss and red cell transfusion may adversely influence post-operative infection rates, length of hospital stay, and mortality[1,2]. There is no agreement on their relative contributions to poor outcomes; however, the preponderance of published evidence suggests some synergy[3].

In a recent analysis of 3,342 patients scheduled for major elective procedures, overall prevalence of anaemia (Hb <13 g/dL) was 36%, and was higher in women than men (53 *vs* 23%, respectively; p<0.001). Over two-thirds of anaemic patients presented with absolute iron or functional iron deficiency (ID). Of note, over one-half of non-anaemic patients presented with ID or low iron stores[4].

The detection and correction of ID constitutes a fundamental strategy within the first pillar of multidisciplinary and multimodal "Patient Blood Management" (PBM) programmes, aimed at ensuring continuity of care to improve clinical outcome[5-8]. Following diagnosis of ID, it is particularly important to identify and address the underlying cause, as well as to select the most appropriate treatment option in order to safely meet patient's needs.

Which is the best route for iron supplementation in surgical patients?

The National Institute for Health and Care Excellence (NICE) in the UK recommends offering oral iron before or after surgery to patients with iron deficiency anaemia[9]. However, oral iron therapy is time-consuming and requires months of treatment to correct perioperative anaemia and replenish iron stores, and it is not always efficacious[10,11], especially in the post-operative period[12]. In the post-operative period, current Italian regulatory guidelines state that when the administration of iron is necessary, an intravenous (IV) therapy is recommended, wherever possible using a single high-dose preparation

for the repletion of iron in storage sites[8]. The European Medicines Agency (EMA) stated that when oral iron cannot be taken or is ineffective in treating iron deficiency (e.g., inflammation, need for rapid iron replacement, on-going blood loss) IV iron is preferred[13]. Most guidelines from professional associations also recommend this approach for the management of perioperative anaemia[7,14-19].

Six different IV iron products are widely used in clinical practice: ferric carboxymaltose (FCM), ferric gluconate (FG), ferumoxytol (FXT), iron isomaltoside 1000 (ISM), iron sucrose (IS), and low molecular weight iron dextran (LMWID) (Table I)[20-27]. As iron is strongly bound to carbohydrates in LMWID, FCM, ISM and FXT, the amount of labile iron is low, allowing the rapid administration of large single doses, leading to fewer hospital visits for patients and therefore lower treatment costs, compared to IS or FG[10,11,28].

What is the risk of a severe adverse event with the administration of intravenous iron?

The medical community has had a long-lasting prejudice against IV iron, irrespective of formulation, due to concerns about the potential for acute, serious adverse events (SAEs) which can lead to anaphylaxis, hypotension, and shock[10,11,29]. However, the overwhelming majority of severe and potentially lethal reactions were due to high molecular weight iron dextran (HMWID) formulations, which are no longer available. When HMWID is excluded, IV iron is associated with an estimated SAE incidence of less than 1 in 250,000 administrations[30]. Compared to the risk of death and acute SAE resulting from transfusion, the risk with IV iron is almost negligible. As estimated from 2012 Serious Hazards of Transfusion (SHOT) data, the risks of death and SAEs were 1 in 322,580 and 1 in 21,413 blood components issued, respectively[31]. Other non-evidence-based concerns regarding IV iron supplementation, such as increased risk of infection, iron overload or oxidative stress, have been also refuted[10,11]. Therefore, the heightened public and regulatory concern about IV iron reactions may need to be reviewed[32].

Risk of infusion reactions

Minor infusion reactions to IV iron are due to labile iron and not to hypersensitivity[33]. They are characterised by chest and back pressure, flushing, itching and/or urticaria, but without accompanying hypotension, tachypnoea, tachycardia, wheezing, and stridor or periorbital oedema. Minor infusion reactions occur in approximately 1:100-250 IV iron administrations[33-35]. The more stable the carbohydrate which binds the iron core, the less likely minor infusion reactions is to occur. Importantly, these should not be misinterpreted as representing acute hypersensitivity, as the EMA has stated that "intravenous iron containing products must also not be used in patients with serious hypersensitivity to other parenteral iron products"[13]. However, there is no evidence on which to base such a recommendation and it is not consistent with published recommendations[28,36,37].

Risk of hypotension

Hypotension during IV iron infusion could be considered as hypersensitivity or vascular reactions to labile iron. In a meta-analysis of 103 trials comparing IV iron with oral iron, no iron or intramuscular iron, there was no increased risk of serious adverse events with IV iron (relative risk [RR]: 1.04; 95% Confidence Interval

Table I - Characteristics of different intravenous iron formulations.

	Iron Gluconate[c]	Iron Sucrose[d]	LMWID[e]	Ferric carboxymaltose[f]	Iron isomaltoside 1000[g]	Ferumoxytol[h]
Brand name	***Ferrlecit®***	***Venofer®***	***Cosmofer® INFeD®***	***Ferinject® Injectafer®***	***Monofer® Monoferro®***	***FeraHeme® Rienso®***
Molecular weight (kD)	289-440	30-60	165	150	150	750
Plasma half-life (hours)	1	6	20	16	20	15
Labile iron (% injected dose)[a]	3.3	3.5	2.0	0.6	1.0	0.8
Maximum single dose (mg) Dilution volume (mL)	125 100	200 200	20 mg/kg 500	20 mg/kg 250	20 mg/kg 500	510 50-250
Infusion time for 1,000 mg (min)[b]	720	300	180[i]	45	45	90

[a]Jahn MR, *et al.*[20]; [b]Including 30-minute (min) post-infusion observation time recommended by the European Medicines Agency[13]; [c]Ferrlecit® summary of product characteristics[21]; [d]Venofer® summary of product characteristics[22]; [e]LMWID, low molecular weight iron dextran; Cosmofer® summary of product characteristics[23]; [f]Ferinject® summary of product characteristics[24]; [g]Monofer® summary of product characteristics[25]; [h]FeraHeme® summary of product characteristics[26]; [i]Although dosage has not been approved by the US Food and Drug Administration or the European Medicines Agency, not serious adverse events were observed in over 5,000 administration of LMWID at doses of 1,000 mg in 250 mL of normal saline over one hour[27].

[95%CI]: 0.93-1.17)[35]. However, the risk of self-limited hypotensive events was increased with IV iron (RR: 1.39 [95%CI: 1.09-1.77]; number needed to harm [NNH], 97 [95%CI: 58-305]), especially when IS was used (RR: 3.01 [95%CI: 1.12-8.11]; NNH: 68 [95%CI: 37-364])[35]. In previous publications, different hypotension rates were reported in patients receiving IS (0.33%), ISM (0.34%), FCM (1.04%), or FXT (1.9%)[38-41].

Hypotensive reactions are likely related to the rapidity of administration and the labile iron content of IV iron formulations. On 29th November 2010, warnings in bold print were included in the FXT label ostensibly due to increased episodes of life-threatening hypersensitivity reactions and clinically significant hypotension. As a result, the label indications were changed to 510 mg over 15 minutes, instead of over 17 seconds[42]. On the other hand, it has been shown that labile iron measured with FXT was approximately one half of that with LMWID[20], which can be given at a dose of 1,000 mg over 1 hour without any problem[27]. Therefore, as prevention of hypersensitivity reactions by reducing the speed of infusion has also been observed with other infusions containing nanoparticles, the reaction is unlikely to be solely due to higher labile iron levels (see below)[37].

Supporting this conclusion, serum levels of platelet activating factor (PAF), a potent biological mediator of hypersensitivity[43], were significantly elevated in patients with acute allergic reactions compared with healthy volunteers (see below). Serum levels of PAF showed a better correlation with severity than either histamine or tryptase. In fact, increased levels of PAF were found in 20%, 66.7%, and 100% of patients with grades 1, 2, and 3 allergic reactions, respectively[44].

Risk of anaphylaxis

As with any intravenously administered product, IV iron formulations carry a small risk of hypersensitivity reactions which can lead to anaphylaxis (<1:250,000 administrations)[39], which can be life-threatening if not promptly treated. The cause of these anaphylactic-type reactions was believed to be Ig E-mediated, as demonstrated in some cases for HMWID[45,46]. In contrast, there has never been any description of circulating anti-bodies against IS, and this seems biologically implausible[47]. It is now believed that complement activation-related pseudo-allergy (CARPA) triggered by iron nanoparticles may be the most common pathogenic mechanism in acute hypersensitivity reactions to current formulations of IV iron[32,34.37].

Nanoparticle medicinal products, such as IV iron, may activate complement which mediate tissue injury through the generation of the anaphylatoxins (C3a and C5a), and the membrane attack complex (C5b-9). Anaphylotoxins then activate mast cells and basophils, whose secretory products (histamine, thromboxanes, leukotrienes and PFA) can cause the clinical features associated with hypersensitivity reactions (bronchospasm, laryngeal oedema, tachycardia, hypo- or hypertension, hypoxia). In severe cases, CARPA may result in loss of consciousness, shock, and cardio-respiratory arrest[37]. As a rapid iron infusion rate is a major risk factor for hypersensitivity reactions, it is also possible that, after rapid injection of IV iron, anaphylotoxin production rate may exceed the clearance rate from the blood, leading to exacerbation of the CARPA pathogenic sequence[32].

The differences in carbohydrate shell and physicochemical properties of IV iron compounds are likely to influence the prevalence of CARPA reactions. A recent study provides evidence that LMWID and FCM, but not IS, FXT or ISM, have complement-activating capacities *in vitro*, and hypersensitivity reactions to these drugs could be CARPA-mediated[48]. However, a meta-analysis of the safety of different IV iron compounds in inflammatory bowel disease patients found that LMWID was associated with the lowest rate of SAEs, which is inconsistent with the hypothesis[49]. Supporting this conclusion was the fact that there was no difference in the incidence of adverse events observed with any formulation compared to any other[35]. Despite the small risk of SAEs, when indicated, the benefits of IV iron outweigh its risks, provided measures are taken to minimise the risk of hypersensitivity reactions[13].

A report from the EMA's Committee for Medicinal Products for Human Use stated that "data on the risk of hypersensitivity comes largely from post-marketing spontaneous reports and the total number of life-threatening and fatal events reported is low" and "although the data show a clear association of intravenous iron medicines and hypersensitivity reactions, the data cannot be used to detect any differences in the safety profile of the different iron medicines"[13]. Similarly, though USA Food and Drug Administration's Adverse Event Reporting System database is a valuable resource for reporting suspected allergic/anaphylactic reactions, it does not allow any conclusions to be drawn about absolute risks and/or relative risks among IV iron products[50].

How can acute reaction to intravenous iron be prevented or minimised?

Intravenous iron should be administered only at facilities where health care staffs are trained to evaluate and manage anaphylactic reactions[13]. In the extremely unlikely event of a serious hypersensitivity reaction, appropriate pharmacological interventions and equipment should be immediately available[13]. In the perioperative setting, this generally refers to hospital

infusion facility/anaemia clinics, post-anaesthesia care units, and hospital wards.

Patients with co-morbidities which increase the risk of hypersensitivity to (e.g., previous mild-to-moderate reaction to IV iron, other drug allergies, severe asthma, eczema, mastocytosis, respiratory or cardiac disease, treatment with hypotensive drugs) or contraindication for IV iron (e.g. previous severe reaction to other IV iron, severe hepatic disease, iron overload, first trimester of pregnancy, active infection) should be identified. In addition, prior to starting IV iron infusion, staff should inform all patients that infusion reactions may occur and ensure that they understand the information provided and the need to call the attending personnel should any symptom appear (Figure 1).

During administration, staff should be familiar with and be adherent to the appropriate maximum dose, dilution volume and infusion speed for each IV iron formulation, as recommended by the manufacturer, though it is advisable to start all infusions at low rates (<50% of recommended rate), increasing this after a few minutes if no infusion reaction occurs[34,37] (Figure 1). An even lower initial infusion rate (10% of the recommended rate during the first 10-15 min) is suggested in patients at risk of hypersensitivity reactions[37]. In contrast, in Europe, a test dose is no longer recommended, as it does not accurately predict reactions to the subsequent IV iron infusion and has never been shown to alter the therapeutic plan[13].

Pre-medication with methylprednisolone (125 mg IV) prior to administration of any IV iron product should be restricted to patients with a history of asthma, inflammatory arthritis or more than one drug allergy (Figure 1). In those with inflammatory arthritis, a short course of prednisone (1 mg/kg per day orally for 4 days) may be added to prevent a flare[51].

Pre-medication with histamine H_1 receptor antagonists has been reported to cause the majority of perceived reactions to IV iron in one large cohort[52]. First-generation histamine H_1 receptor antagonists (diphenhydramine, dexchlorpheniramine) can cause somnolence, diaphoresis, hypotension and tachycardia ostensibly attributed to the administered IV iron. Tryptase levels, a marker of mast cell degranulation, are virtually always normal, and subsequently the use of these antihistamines to prevent or treat IV iron infusion reaction should be proscribed[36].

The EMA recommends close monitoring for signs of hypersensitivity during and for at least 30 min after every administration of an IV iron product[13] (Figure 1). In contrast, the Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference considered that there is no physiological basis for such a recommendation, since IV iron delivery should not be associated with a severe delayed reaction[34]. However, the day after the infusion, up to 10% of patients may complain of arthralgias and myalgias, which abate spontaneously or with an non-steroidal anti-inflammatory drug[33].

How should acute reactions to intravenous iron be managed?

In the event of a reaction during IV iron administration, the very first intervention should be immediate cessation of the infusion, and to call the attending physician to evaluate its severity and start immediate treatment. The intensity of treatment should be scaled to the clinical picture and/or the response to initial therapy (Figure 1). The hypersensitivity reaction to IV iron can either respond promptly to treatment or progress to a more severe form. Therefore, close monitoring during reaction management and for up to 24 hours after its resolution, depending on the reaction severity and the patient's condition, may be indicated (Figure 1).

Usually, minor infusion reactions are mild and abate spontaneously within 5-10 min without any intervention and rarely recur with re-challenge at lower infusion rate, especially if the patient has been pre-medicated with steroid prior to re-challenging[53] (Figure 1). If symptoms recur during re-challenge, switching to another IV iron formulation is appropriate (Figure 1). For example, IS was reported to be well tolerated by haemodialysis patients with previous reactions to other IV iron formulations[54]. Thus, aggressively treating non-allergic infusion reactions with H_1 antihistamines (diphenhydramine) or vasopressors (epinephrine) should be avoided as diphenhydramine or vasopressors may convert this mild reaction to a more serious adverse reaction, erroneously attributed to the IV iron[53].

If there are non-specific symptoms which include urticaria, treatment with antihistamines and/or corticosteroid may be considered. Second generation antihistamines are more selective for peripheral H_1 receptors and bind to fewer central nervous system histaminergic and cholinergic receptors. This selectivity significantly reduces the adverse reactions, especially sedative effects, compared with those of the first generation (diphenhydramine), although they continue to provide effective relief of allergic disorders. Thus, second (ebastine, loratadine, cetirizine) or third (levocetirizine, desloratadine) generation H_1 antihistamines are first-line medications for the treatment of acute urticarial reaction and angioedema, but it is important to note that their administration is exclusively via oral administration or in aerosol[55-57]. The limited evidence from small studies suggests that H_2 antihistamines (ranitidine or cimetidine), which can be administered parenterally,

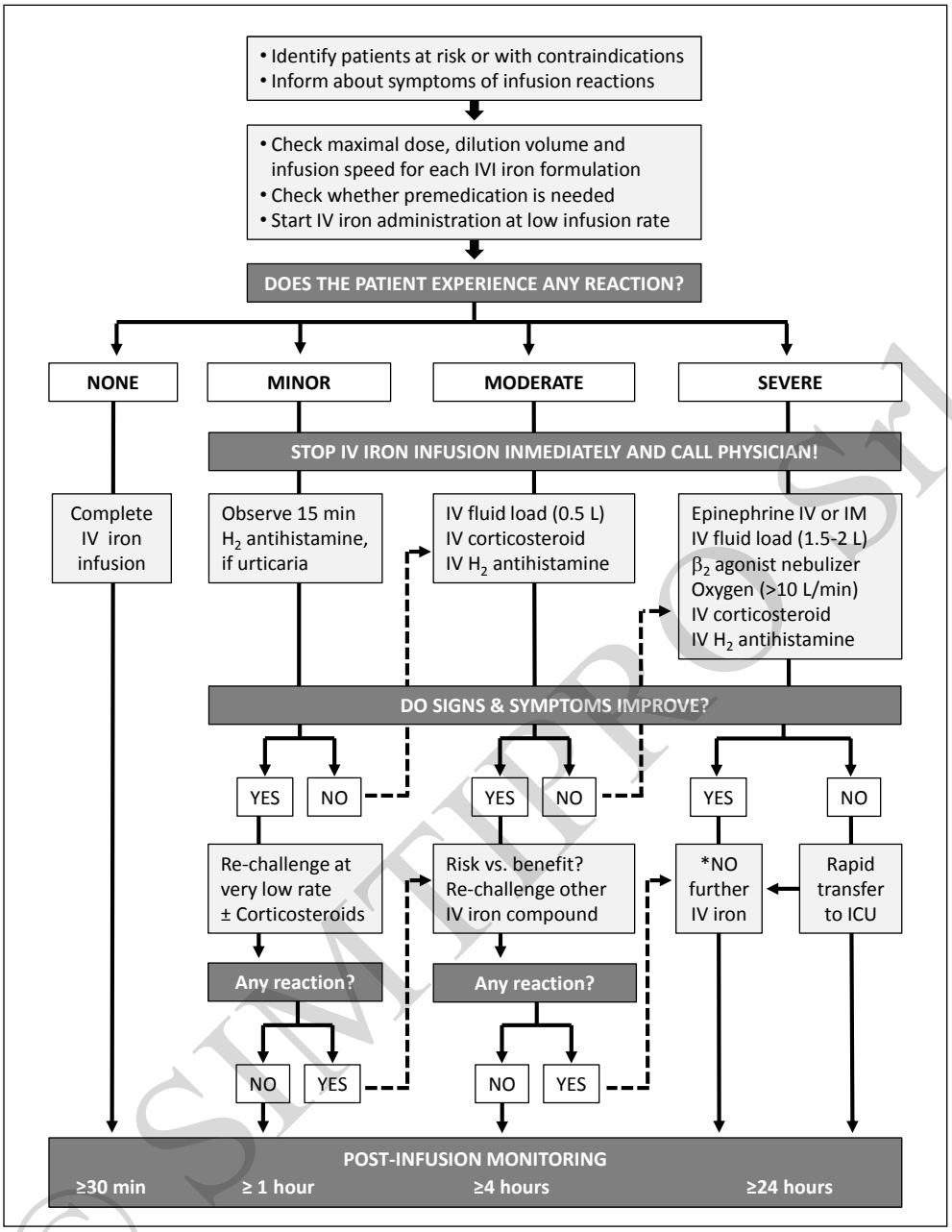

Figure 1 - An algorithm for prevention and management of reactions to intravenous iron administration (Based on Macdougall *et al.*[34] and Rampton *et al.*[37]).
ICU: intensive care unit; IV: intravenous; IM: intramuscular; IV IRON: intravenous iron; (---) consider scaling to the next treatment step. *According to European Medicines Agency recommendation[13].

resulted in similar improvement in itching and wheal size, and intensity when compared to diphenhydramine[58]. Thus, IV H_2 antihistamines could be preferred for treating an urticarial reaction to IV iron (e.g. rainitidine 50 mg). In severe cases, IV hydrocortisone (100 mg) or methylprednisolone (40-80 mg) may be started initially, followed by oral prednisone or prednisolone (0.5-1 mg/kg/day) for 3-10 days to control symptoms[34,37,59].

If tachycardia and hypotension develop, the patient should be laid horizontally with leg elevation and receive an IV isotonic crystalloid load (e.g. 500 mL). Cardiac frequency, arterial pressure, ECG, and oxygen saturation should be continuously monitored. Although not clearly evidence-based, IV corticosteroid (hydrocortisone 100-500 mg) and IV H_2 antihistamine can be considered. Once the reaction abates, re-challenging with a different IV iron compound could be considered after a careful evaluation of the benefit-risk ratio (Figure 1).

By definition, anaphylaxis has cardiovascular and respiratory manifestations, and therefore epinephrine (0.5 mg 1/1,000 IM or 0.1 mg 1/10,000 IV) is the first-line treatment, and should be administered as soon as a diagnosis is suspected[26,29,60] (Figure 1). Overuse of antihistamines, which do not treat cardiovascular or respiratory manifestations of anaphylaxis, can delay the effective first-line treatment with epinephrine, a situation which has been associated with fatalities during anaphylaxis[60]. Additional therapeutic measures include IV isotonic crystalloid load (e.g. 1,000-2,000 mL) and nebulised β_2-adrenergic agonist and/or ipratropium with high rate oxygen rate (10-15 L/min, according to pulse oximetry) to combat wheezing, initially by face mask (but the staff should be prepared for the possible need for fiberoptic intubation with the patient awake)[61] (Figure 1). A Cochrane review found no evidence for the effectiveness of corticosteroids in anaphylaxis[62]. However, as corticosteroids have short-term effects and may be beneficial in selected patients, administration of IV hydrocortisone (100-500 mg) or methylprednisolone (1-2 mg/kg) is common practice[34,37,57,63] (Figure 1). The on-site advanced cardiac and life support team should implement standard protocols in the event of cardiac or respiratory arrest, and the patient be rapidly transferred to the intensive care unit if there is no immediate and complete response.

Importantly, any reaction to IV iron should be appropriately documented (including the brand name of the product) and reported to the national pharmacovigilance system[37]. According to EMA recommendations, future administration of any IV iron formulation is contraindicated in patients experiencing a severe hypersensitivity reaction to any of them[13] (Figure 1). While a cogent recommendation, there is no evidence to support this.

Conclusions

In surgical patients, screening, diagnosing and treating anaemia improve postoperative outcomes and promote patient well-being[64,65]. Iron deficiency is the leading cause of perioperative anaemia. The objective of successful treatment of iron deficiency anaemia is the adequate and prompt supply of iron to increase haemoglobin levels and to replenish iron stores.

Intravenous iron has being earning an undeniably important role in the management of iron deficiency in PBM programmes due to the large amount of available clinical data on its efficacy and safety. When time for diagnosis and treatment is very limited, use of oral iron means the surgical patient is denied the opportunity to receive successful therapy as this can only be accomplished with IV iron. In this situation, it is essential to use IV iron; failure to administer it is not only counterproductive but potentially harmful[36].

Most available evidence supports the conclusion that there is no difference between the safety profiles of the different available formulations[16]. Severe adverse events due to IV iron administration, including mortality, are exceedingly rare but should not be ignored[66]. Therefore, IV iron should only be administered under the supervision of staff trained to evaluate and manage severe hypersensitivity reactions, following a clear-cut algorithm, and where resuscitation facilities are immediately available.

Authorship contributions

All the authors meet all of the following four conditions: 1) substantial contribution to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published.

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