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Iron deficiency anemia from diagnosis to treatment in children

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Abstract

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Iron deficiency is the most common nutritional deficiency worldwide and an important public health problem especially in developing countries. Since the most important indicator of iron deficiency is anemia, the terms “iron deficiency” and “iron deficiency anemia” are often used interchangeably. However, iron deficiency may develop in the absence of anemia and the tissues may be affected from this condition. The most common causes of iron deficiency in children include insufficient intake together with rapid growth, low birth weight and gastrointestinal losses related to excessive intake of cow’s milk. If insufficient intake can be excluded and there is insufficient response to oral iron treatment in patients with iron deficiency especially in older children, blood loss should be considered as the underlying cause. The main principles in management of iron deficiency anemia include investigation and elimination of the cause leading to iron deficiency, replacement of deficiency, improvement of nutrition and education of the patient and family. In this article, the practical approaches in the diagnosis and treatment of iron deficiency and the experience of our center have been reviewed.

Keywords: Anemia, child, iron deficiency

Introduction

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Iron deficiency is the most common nutritional deficiency worldwide and an important public health problem especially in developing countries. There is no clear data about how many individuals are affected by iron deficiency worldwide, but it is estimated that ID is present in most of the pre-school children and pregnant women in developing countries and in at least 30–40% in developed countries when anemia is used as an indirect indicator of ID (1). According to the 2001 World Health Organization (WHO) data, 30% of the children aged between 0 and 4 years and 48% of the children aged between 5 and 14 years are anemic in developing countries (1). In our country, the frequency of iron deficiency anemia (IDA) has been reported to range between 15.2% and 62.5% in different studies conducted with children (2–5).

Since anemia is the most important indicator of iron deficiency, the terms ID and IDA are often used interchangeably. However, iron deficiency may develop in the absence of anemia and the tissues may be affected from this condition. Iron deficiency is manifested in different stages. If iron requirement is below intake, iron stores are reduced primarily. After the iron stores are reduced, hemoglobin levels may stay normal for a while which means that iron deficiency is observed in the absence of anemia. At this time, only plasma ferritin level and plasma transferrin saturation are reduced. Negative iron balance which continues after iron stores are exhausted is manifested with decreased hemoglobin. Conclusively, reduced body iron stores has been defined as ID and

worsening of this condition and development of anemia is defined as IDA.

Reduced erythrocyte count or a hemoglobin (Hb) value 5 percentile below the normal hemoglobin value specified for that age in healthy individuals is defined as anemia. When defining anemia, the lower limit of the normal value for different age groups and genders should be determined. Iron deficiency anemia is the most common cause of anemia in the world and in our country. In the childhood, it is most frequently observed in infancy and in adolescents who have menstruation, but any child with increased growth rate and children whose requirements are not met adequately are under risk.

In this article, the significant points in diagnosis and treatment of iron deficiency which is one of the most common diseases observed in children have been compiled in terms of directing pediatricians, the recent studies performed in this area have been reviewed and the experiences of our center have been explained.

Etiology

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The most common causes of IDA observed in children include inadequate intake together with rapid growth, low birth weight and gastrointestinal losses due to excessive consumption of cow's milk. In the intrauterine period, the only source of iron is iron crossing through the placenta. In the final period of pregnancy, the total amount of iron in the fetus is 75 mg/kg. Physiological anemia develops in the postnatal period and iron stores are sufficient to provide erythropoiesis in the first 6 months of life if there is no significant blood loss. In low birth weight infants and in babies with perinatal blood loss, the stores are exhausted earlier, since they are smaller. Delayed umbilical cord clamping may improve the iron status and reduces the risk of iron deficiency (6). The amount of iron in breastmilk is at the highest level in the first month, but it decreases gradually in the subsequent periods and is reduced up to 0,3 mg/L approximately at the fifth month (7). Yet, this amount varies from individual to individual. It has been shown that maternal diet does not affect the amount of iron in breastmilk (8). Although the amount of iron received from breastmilk is typically low, its absorption is considerably high (50%). It is known that other foods given during the first 6 months in addition to breast-milk disrupt absorption of iron in breastmilk. Therefore, these foods should be given at separate meals. Conclusively, the absorption is high, but it is lower than the amount required for growth. Thus, infants use the iron in their iron stores in the first 6 months until the amount of iron received from foods increases.

Solid foods given after the 6th month should be rich especially in iron, zinc, phosphorus, magnesium, calcium and vitamin B6. According to the world Health organization data, 98% of the iron requirement in infants aged 6–23 months should be met by solid foods (9, 10). Solid foods should include products rich in meat, fish, egg and vitamin C to meet this iron need. Another mistake made in feeding infants is giving excessive cow's milk at an early time. In infants, chronic blood loss may be observed in relation with heat-sensitive proteins in cow's milk. In addition, the absorption of iron in cow's milk is much lower compared to breastmilk. Cow's milk will substitute for iron-rich foods and in addition calcium and caseinophosphopeptides in cow's milk may disrupt the absorption of iron. If infants are fed with iron-poor foods after the 6th month when they exhaust almost all of their iron stores, iron deficiency develops easily.

In patients and especially in older children, blood loss as an underlying cause should be considered, if inadequate intake can be excluded or there is inadequate response to oral iron treatment. Chronic iron deficiency anemia which develops with occult bleeding is observed with a relatively lower rate in children and may occur as a result of gastrointestinal problems including peptic ulcer, Meckel's diverticulum, polyp, hemangioma or inflammatory bowel disease. Insensible blood loss may rarely be related with celiac disease, chronic diarrhea or pulmonary hemosiderosis; it is possible to make the differential diagnosis with history. It should be kept in mind that parasitosis may also contribute to iron deficiency especially in developing countries. Iron deficiency anemia is observed in 2% of adolescent girls and it is mostly related with growth spurt and menstrual blood loss (11). A detailed history of menstruation should be obtained in adolescent girls and underlying bleeding disorders including von-Willebrand

disease should be kept in mind in girls who have bleeding in excess than expected.

Clinical findings

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Since the majority of iron in the body is used for synthesis of hemoglobin, the most important finding of iron deficiency is anemia. In iron deficiency anemia, clinical findings secondary to anemia may be found as in all anemias or the diagnosis can be made during laboratory investigations in the absence of any clinical finding. Slowly progressing paleness may sometimes be missed by families. The clinical findings observed in iron deficiency anemia are summarized in [Table 1](#). The finding which is mostly emphasized in iron deficiency anemia is its effects on the neurocognitive system. Many well-designed prospective studies have shown that motor and cognitive retardation and mood disorders may be observed in children with iron deficiency ([12–14](#)). Lozoff et al. ([15](#)) showed that children with iron deficiency got tired more easily, played less and were more hesitant compared to completely healthy children. More importantly, these effects persisted 10 years after treatment ([16](#)). ID which has progressed to iron deficiency anemia may cause to disruption in mental and motor functions and these effects may be permanent. The mechanism of action by which iron deficiency causes to neurocognitive disorders is not fully understood. In some studies, it was shown that ID decreased expression of dopamin receptors, disrupted myelination or disrupted the function of various enzymes involved in the nerve tissue ([17–19](#)). Again, another important yet controversial clinical effect of iron deficiency is its effects on the immune system ([20–22](#)). In addition, it was shown that IDA was strongly related with febrile convulsions in some recent studies and in a meta-analysis performed in 2010 ([23, 24](#)).

[Table 1.](#)
Iron deficiency findings

Diagnosis and laboratory findings

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In medicine, a detailed history and physical examination is essential in the diagnosis of all diseases as a general rule. In one study, it was shown that anemia could be diagnosed with a detailed history with a sensitivity of 71% and specificity of 79% ([25](#)). Especially prenatal period, nutrition, times of starting breastmilk and solid foods and bleeding history should be interrogated in detail. Signs of anemia and other systemic diseases which may accompany should be searched for.

The laboratory tests which may be used are summarized in [Table 2](#). The primary action is ordering complete blood count and peripheral blood smear. When complete blood count is assessed well, it may give many clues in the diagnosis of many diseases of the childhood ([26](#)). In complete blood count, it should be primarily checked if hemoglobin and hematocrit values are normal for age and gender (if anemia is present). The lower limits of normal by age and gender specified by the World Health Organization may be used, since they are practical and values lower than these limits are considered anemia ([Table 3](#)). In infants younger than 6 months, lower values are observed because of physiological anemia, but hemoglobin is not expected to be lower than 9 g/dL in physiological anemia in term infants if there is no other accompanying factor.

[Table 2.](#)
Investigations which may be ordered in patients in whom iron deficiency is considered

[Table 3.](#)
Lower limits for hemoglobin and hematocrit values specified by the World Health Organization by age and gender

Erythrocytes appear pale and smaller than normal when the amount of hemoglobin inside is reduced. This is manifested by reduced mean erythrocyte volume (MCV) and reduced mean erythrocyte hemoglobin (MCH) in complete blood count. On peripheral blood smear, the erythrocytes are microcytic and hypochromic. Mean erythrocyte volume and MCH are parallel to each other; this means that microcytic erythrocytes are hypochromic at the same time. If the MCH is below 27 pg, it is low. The normal value of mean erythrocyte volume ranges between 80 and 99 fL, but normal values by age should be considered in children. Formulas which may be used simply in busy outpatient clinical practice are also present ([Table 4](#)). Here, it is important to use the formula for the lower limit for children younger than 10 years, because the lower limit is 80 fL in children older than 10 years as in adults.

Parameter	Normal Range	Iron Deficiency Range
MCV (fL)	80-100	<80
MCH (pg)	27-32	<27
MCHC (g/dL)	32-36	<32

[Table 4.](#)

Laboratory findings in iron deficiency

In anemias related with nutritional deficiencies, there is a non-homogeneous erythrocyte volume in contrast to congenital anemias including thalassemia; erythrocytes may have variable sizes according to the amount of hemoglobin. This is reflected by anisocytosis on peripheral smear and by increased erythrocyte distribution width (RDW) on blood count. Basically, nutritional deficiency should be considered, if increased RDW together with anemia is present; if reduced MCV is also present, iron deficiency is considered and if increased MCV is present, vitamin B12 or folic acid deficiency may be present. However, it should be kept in mind that withdrawal or deficiency anemia where all variables are disrupted is not observed rarely in most children with malnutrition. A normal RDW value and microcytosis suggest thalassemia carrier state rather than iron deficiency anemia. Generally, two separate RDW results are noted in complete blood count results; RDW-CV and RDW-SD. This arises from a statistical calculation difference. RDW-SD is the standard deviation of the erythrocyte and is the mean of deviations from MCV of each erythrocyte; its normal range is 37–54 fL. RDW-CV is the variability coefficient of erythrocyte distribution volume and the percentage expression of the standard deviation by mean erythrocyte volume. RDW-CV is a more reliable measurement and is abnormal if it is >14. In addition, erythrocyte distribution width is the first variable which changes in complete blood count in iron deficiency anemia. In parallel, the first finding of IDA on peripheral smear is anisocytosis.

Hemoglobin distribution width (HDW) is a variable which is not noted by most individuals in complete blood count results. It shows the distribution of the hemoglobin in the erythrocytes and is increased in iron deficiency. This is reflected as anisochromia on peripheral smear. The mean erythrocyte hemoglobin concentration is measured indirectly by hemocounter devices and is classically reduced in iron deficiency. It is also important to draw attention to the erythrocyte count in complete blood count. While the erythrocyte count is increased in thalassemias characterized with inefficient erythropoiesis (production of erythrocytes is increased, but destruction takes place in the bone marrow before the cells enter the peripheral blood), it is reduced in iron deficiency anemia because of insufficient production. A formula which is obtained using the erythrocyte count and MCV value may be beneficial in differentiating IDA from thalassemia carrier state. While MCV is reduced both in thalassemia carrier state and IDA, the erythrocyte count is reduced in IDA, but increased in thalassemia carrier state. In this case, the MCV/RBC ratio is higher in IDA because RBC is reduced and it is lower in thalassemia carrier state because the RBC value is higher. As a result of this formula which is called the Metzner index, thalassemia is considered when this ratio is below 13 and IDA is considered when this ratio is above 13.

In addition, thrombocytosis in relation with IDA may be observed in complete blood count. The reason of thrombocytosis is cross-reaction of increased erythropoietin in IDE with thrombopoietin receptors in the megakaryocytes which leads to increased platelet count. Although rarely, thrombocytopenia may also be observed in IDA ([27](#)). The leukocyte count is usually normal, but leukopenia may also be observed. However, other

diagnoses should be considered primarily in cases of anemia especially accompanied by leukopenia and/or thrombocytopenia. Eosinophilia in complete blood count or peripheral smear may give a clue in terms of underlying parasitosis. At this point, treatment can be started directly, if complete blood count and peripheral smear strongly suggest IDA. If there is suspicion, treatment itself is a good diagnostic tool. However, ordering iron variables at the baseline is a better scientific approach; further it will be valuable for differential diagnosis and if anemia will not respond to iron treatment. In fact, hemogram may be sufficient in the diagnosis of IDA, but it may be normal in the early stages of iron deficiency. Iron deficiency develops in the body in three stages.

1. **Prelatent stage:** Iron stores are lowered or absent, serum iron concentration, hemoglobin and hematocrit are normal. This stage of iron deficiency is manifested with reduction or absence of bone marrow iron stores and reduced serum ferritin level.
2. **Latent stage:** serum iron (SI) and transferrin saturation are reduced in addition to reduced iron stores. Hemoglobin and hematocrit are within normal limits.
3. **Marked IDA:** In addition to the depletion of iron stores, serum iron and transferrin saturation hemoglobin and hematocrit levels are reduced.

All variables may not change at the same time because of development of these stages in children with iron deficiency. One should be very careful when evaluating iron variables. The serum ferritin level is the best indicator of the iron stores in the body and the first biochemical variable to change in ID. A serum ferritin level below 10–12 µg/L strongly supports ID, but ferritin is an acute phase reactant and it should be kept in mind that it may be increased in infection and inflammation. Plasma iron is reduced as the iron in the body is exhausted. Samples should be obtained in the morning after one- night fasting, because its value shows variance during the day time and is affected by diet. Plasma iron level is not helpful in the differential diagnosis from IDA because it is also reduced in anemia of chronic disease. Iron binding capacity (total iron binding capacity-TIBC) increased as serum iron decreases. The value obtained by dividing the serum iron value to TIBC shows transferrin saturation and is reduced in ID. Iron and TIBC are also acute phase reactants and increase in inflammation/infection.

Some new methods have been developed to be used in definite diagnosis because of some defects of hematological and biochemical tests. Additional tests including zinc protoporphyrin (ZnPP), free erythrocyte protoporphyrin, serum soluble transferrin receptor (sTfR) and reticulocyte hemoglobin content may be helpful (28). The diagnosis will be delayed when the hemoglobin content of the erythrocytes are measured, because the life span of normal erythrocytes is 120 days. Reticulocyte hemoglobin content reduces earlier, because the reticulocyte life span is 24–48 hours. In some studies, it was shown to be the most sensitive variable in the diagnosis of IDA, but its most important limitation for Turkey is the fact that it is also reduced in thalassemia carrier state. Serum transferrin receptor can be tested by immunoassay method in some laboratories. This receptor is found on reticulocytes and an increase is observed in transferrin receptors in IDA. Zinc protoporphyrin is produced with substitution of zinc instead of iron when iron is absent and thus is increased in IDA. Since bone marrow is the first place where serum iron is reduced, bone marrow aspiration is gold standard in IDA, but is not used routinely. In some cases, a definite diagnosis can be made only by combined use of multiple tests. The reticulocyte count may be normal or low. Urea and creatinine values should be checked in terms of accompanying renal failure especially in patients who do not adequately respond to treatment. The laboratory findings in iron deficiency are summarized in [Table 4 \(29–32\)](#).

Prevention

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The American Academy of Pediatrics, the World Health Organization and other well-known pediatrics organizations have proposed many recommendations for prevention of iron deficiency which is the most common nutritional deficiency in the whole world. These recommendations include enrichment of foods with iron, giving iron-rich formulas when breastmilk is insufficient, avoiding cow's milk in the first year of life, screening infants in the 9–12th months in terms of iron deficiency and giving infants iron prophylaxis (33).

Each of these methods have controversial points. Since anemia will develop in the advancing stages of iron deficiency, many children with ID will be missed in screenings performed at the 9–12th months only by complete blood count and irreversible neurocognitive changes will already have developed. Food enrichment is addition of deficient micronutrients to solid food products. Enriched food should be consumed by everybody, but this is not always possible especially for poor individuals and for individuals who live in rural areas. Technical problems including taste changes and decreased bioavailability may also be observed in relation with enrichment of food products (34). Iron prophylaxis is also a controversial issue. Many contrary views were proposed when the American Academy of Pediatrics recommended prophylaxis in 2011 for term infants who were breastfed (35, 36). In some studies, the benefit of prophylaxis with iron drops was found to be inadequate when compared with supplement with food products or formulas (37, 38). The most ideal way in meeting the requirement of iron and other micronutrients is improvement of the quality of food products. Especially increasing consumption of animal products will meet many requirements including iron. However, consumption of meat is considerably low in developing countries and consumption of unleavened bread including pastry and thin bread, cereal, flour is high traditionally. For many Turkish families tea is indispensable. In one study we performed, we showed that iron stores were reduced in the follow-up despite recommendations for infants aged 6–9 months who switched to solid foods after receiving breastmilk for the first 6 months (39).

Conclusively, the preventive measures on which a consensus was made include prevention of premature delivery, delayed clamping of the cord especially in premature babies, exclusive breastfeeding in the first 6 months, giving solid foods in addition to breastmilk at separate meals, avoiding cow's milk before one year of age, use of iron-enriched formulas if formula milk is to be used instead of breastmilk and using solid foods which are especially rich in heme iron.

Treatment

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The main principles in treatment of iron deficiency anemia include making the diagnosis, investigating the condition which causes to iron deficiency and elimination of this condition, replacement of deficiency, improvement of nutrition and education of patients and families. Iron is found in two forms in diet; non-heme iron and heme iron. Non-heme iron is found in food products other than meat and heme iron is found in meat and meat products. Absorption of heme iron is much higher, but only 10% of the iron in diet is heme iron. While the absorption of heme iron is affected by environmental factors with a very low rate, non-heme iron is affected by other food substances and pH of the environment. Therefore, increasing consumption of meat and meat products is very important in prevention and treatment of iron deficiency. The other foods rich in iron include egg, well-done legumes, green vegetables and dry fruit.

The literature contains an insufficient number of publications related to iron treatment. A reason for this is the fact that mild iron deficiency is not noticed adequately and less priority is given to the researches performed to improve IDA treatment. There are many different recommendations related with the dose, content, period and follow-up of iron treatment in different publications. As a result of this, many physicians administer very low doses of iron or inappropriate iron content and treatment fails or many patients discontinue treatment because of side effects related with high dose. There are many different iron preparations with different content in the market and some of them are called food supplements and are under supervision of the Ministry of Food, Agriculture and Livestock. Oral iron treatment is preferred primarily because it is economical and has few side effects. Iron preparations may be found as +2 ferrous or +3 ferric forms. The ferric form has to be transformed into the ferrous form to be absorbed. Therefore, the biologically significant form is +2 ferrous iron. The most commonly used oral +2 ferrous iron preparations include ferrous sulphate, ferrous gluconate, ferrous fumarate and ferrous succinate. The first study about this issue was performed by Nathan Smith (40) in 1950, the most inexpensive and efficient one among 1970 iron preparations was shown to be ferrous sulphate. Ferrous sulphate is still the most commonly used preparation; the reason for this may be the insufficient number of studies performed since that time. Absorption of ferrous

sulphate (ferrous sulphate complex: an example in Turkey is Ferrosanol[®]) is very well and its bioavailability is high, but it may have side effects including irritation in the gastrointestinal system, constipation, nausea, vomiting and epigastric pain. In our country, drop and suspension forms are present : Ferrosanol[®] 1 drop: 1 mg, 1 spoon: 20 mg elementary iron. In addition, pill (40 mg elementary iron) and capsule (100 mg elementary iron) forms are also present for older children.

The most commonly used treatment dose is 3–6 mg/kg/day. There are different recommendations related to the dose, in the literature and textbooks. For example, the recommended dose is 3 mg/kg in Nathan and Oski's hematology testbook, 4.56 mg/kg/day in Lanzkowsky's Pediatric Hematology Oncology testbook and 6 mg/kg/day in Williams' Hematology testbook. The Centers for Disease Control in USA recommended use of 3 mg/kg/day elementary iron in 1998 in order to simplify the dose and increase compliance, but this recommendation is based on expert opinion rather than clinical studies. In our own center, we give 3–4 mg/kg/day ferrous iron in two doses 1 hour before or 2 hours after meals in order to increase compliance. There are also different recommendations in relation with dividing the dose. Studies have shown that a single daily dose was also efficient especially in children who developed gastrointestinal side effects (41). Further, different administration methods are also being discussed. It is thought that iron consumed one day before disrupts the absorption of iron consumed next day, makes mucosal inhibition. Therefore, every other day or weekly treatments is also being discussed. In a study performed in our center in recent years, no difference was found between the efficiencies of daily and weekly iron treatments (42, 43).

It is known that ascorbic acid increases absorption of iron, but use of preparation containing vitamin C in combination with iron has a high cost. In Turkey, ferrous fumarate is included in another preparation containing +2 iron for children. It has two forms one of which contains zinc, vitamin C, folic acid and iron and the other one which contains only zinc and iron (Ferrozinc[®], Ferrozinc-G[®], respectively 1 spoon: 40 mg elementary iron). In a thesis study performed in our center, we showed that zinc deficiency accompanied iron deficiency with a rate of 9% (44). However, there are no sufficient studies related with routine addition of zinc to iron preparations. We think that use of preparations containing iron and zinc will be beneficial in areas where malnutrition is present and in children with iron deficiency together with growth and developmental retardation, delayed wound healing and frequent infections because of immune system disorder even serum zinc levels could not be measured due to insufficient laboratory opportunities.

The rate of iron absorption also depends on the severity of anemia. It reaches the highest values in the first month of treatment. Signs observed in patients including restlessness, loss of appetite and fatigue rapidly disappear with initiation of treatment. An increase in the reticulocyte count is expected on the 7–19th days of treatment. If an increase of 1 g/dL or more is observed in Hb after ten days, the diagnosis is correct. In this case, treatment can be continued for at least 2 months to fill iron stores. The treatment period should not exceed 5 months. If there is an insufficient increase after one-month treatment, incompliance, continuing blood loss despite iron replacement, disruption in absorption of iron, high gastric pH (use of antacids or H₂ receptor antagonists), wrong diagnosis or inefficient iron preparation should be considered.

Parenteral iron treatment can be administered when oral iron treatment can not be tolerated, in cases where anemia should be corrected rapidly and in gastrointestinal absorption disorders including celiac disease or inflammatory bowel disease. There are not many studies conducted with children comparing parenteral and oral iron treatment in IDA related with nutritional deficiency and more studies are needed in this area. Since adverse effects were observed with a high rate with the first parenteral iron preparations which came onto the market, a hesitancy occurred among physicians, but the iron preparations which have been available on the market in recent years are more reliable and adverse side effects are considerably few. However, it should be kept in mind that these side effects are severe when they develop. Allergy, anaphylaxis, hypotension, nausea, vomiting and abdominal pain may develop especially following rapid infusion. A test dose should be administered before low molecular weight iron dextran. This is not necessary for the other drugs. Pretreatment with antihistaminics and steroid is only required for patients

with a history of drug allergy or asthma. Another disadvantage of parenteral iron preparations is the fact that they are more expensive compared to oral treatment. Correction of anemia with parenteral treatment is not faster compared to oral treatment. Parenteral iron treatment is administered by intramuscular (im) or intravenous (iv) route. In our clinic, we mostly prefer iron sucrose (Venofer®). Since administration of high dose at once may cause to hypotension, abdominal pain, vomiting and diarrhea, the patient should come on consecutive days and receive treatment. The protocol used in our clinic for parenteral iron requirement is shown in [Table 5](#). Blood transfusion has no place in the treatment of IDA except in congestive heart failure.

[Table 5.](#)

Cerrahpaşa Medical Faculty intravenous iron treatment protocol

Conclusively, iron deficiency anemia continues to be a significant public health problem in the world and in Turkey. Practical diagnostic and therapeutical approaches and the experiences of our center have been reviewed in this article. Low-cost, rational and randomized-controlled studies investigating the main variables including dose, side effects, compliance and treatment period are needed for the better out comes in IDA.

Footnotes

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Peer-review: Externally peer-reviewed.

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