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ORIGINAL ARTICLE

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The management of anemia in pediatric peritoneal dialysis patients

Guidelines by an ad hoc European committee

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Abstract Anemia is common in chronic renal failure. Guidelines for the diagnosis and treatment of anemia in adult patients are available. With respect to the diagnosis and treatment in children on peritoneal dialysis, the European Pediatric Peritoneal Dialysis Working Group (EPPWG) has produced guidelines. After a thorough diagnostic work-up, treatment should aim for a target hemoglobin concentration of at least 11 g/l. This can be accomplished by the administration of erythropoietin and iron preparations. Although there is sufficient evidence to advocate the intraperitoneal administration of erythropoietin, most pediatric nephrologists still apply erythropoietin by the subcutaneous route. Iron should preferably be prescribed as an oral preparation. Sufficient attention has to be paid to the nutritional intake in these children. There is no place for carnitine supplementation in the treatment of anemia in pediatric peritoneal dialysis patients.

Keywords Peritoneal dialysis · Children · Erythropoietin · Iron · Carnitine

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The treatment of anemia in chronic kidney disease has been summarized in the NKF/DOQI guidelines [1], which have recently been updated [2]. European best practice guidelines have also been recently published [3]. These published guidelines pay no, or very limited, attention to the special situation in children.

The European Pediatric Peritoneal Dialysis Working Group (EPPWG) was established in 1999 by pediatric nephrologists with a major interest in peritoneal dialysis and has, among other things, published guidelines on commencing elective chronic peritoneal dialysis [4]. One of the functions of the group is to establish expert guidance in important clinical areas associated with peritoneal dialysis in conjunction with other members of the multidisciplinary team. These guidelines were initiated and discussed at meetings of the group and developed by e-mail discussion to develop a consensus of opinion based upon cumulative clinical experience and reported studies. The present guidelines apply to the management of anemia in pediatric peritoneal dialysis patients.

Definition of anemia

More than in adult patients, hemoglobin and hematocrit values are age dependent in children [5], (Tables 1, 2, 3, 4). Also, concentrations of ferritin, transferrin, and iron are dependent on age. Early iron deficiency may be diagnosed by an increase in hypochromic red blood cells [6]. The technique for measuring this parameter is not available everywhere. Since children with renal failure gener-

Table 1 Reference ranges of anemia parameters in children [5]: hemoglobin and hematocrit (*M* male; *F* female)

	Hemoglobin (g/dl)	Hematocrit (%)
1–3 days	14.5–22.5	45–70
2 months	9.0–14.0	28–42
6–12 years	11.5–15.5	35–45
12–18 years, M	13.0–16.0	37–49
F	12.0–16.0	36–46

Table 2 Reference ranges of anemia parameters in children [5]: ferritin

	Ferritin (ng/ml)
Newborn	25–200
1 month	200–600
2–5 months	50–200
6 months–15 years	7–140

Table 3 Reference ranges of anemia parameters in children [5]: iron (*M* male; *F* female)

	Iron (μg/dl)
0–2 months	100–250
2–12 months	40–100
1–12 years	50–120
Thereafter, M	50–160
F	40–150

Table 4 Reference ranges of anemia parameters in children [5]: transferrin

	Transferrin (mg/dl)
Newborn	130–275
Adult	200–400

ally do not have underlying co-morbidity contributing to anemia, it is obvious that in children on peritoneal dialysis normal hematocrit levels should be aimed for (*opinion*). The work-up of the anemic child is not different from the work-up that is advocated for adult patients by the DOQI guidelines, although the importance of a stool test for occult blood may be less useful in this age group [2, 7] (*opinion*):

- Iron deficiency
- Clinical history
- Assessment of nutritional status
- Hemoglobin and hematocrit
- Red blood cell indices
- Reticulocyte count
- Iron parameters
- Serum iron

After this work-up has been completed, iron and/or erythropoietin therapy should be initiated to obtain a target hemoglobin concentration of at least 11 g/dl (hematocrit 33%), although there is a tendency to increase this target [8] (*opinion*).

A target hemoglobin concentration of at least 11 g/l should be aimed for in children on peritoneal dialysis (*opinion*).

Erythropoietin

Most experience has been obtained with subcutaneous administration of recombinant human erythropoietin [9, 10]. Erythropoietin is available as erythropoietin alpha and beta. Erythropoietin alpha and beta differ noticeably in their formulation excipients. No clear prescription schedules for starting erythropoietin are available for children, and schedules provided in the literature vary greatly. It seems reasonable to start with a subcutaneous dosage of 50–100 U/kg body weight 2 or 3 times per week. In some selected patients (particularly if started in the predialysis period) a lower frequency or dosage can be attempted. In studies in adult patients once weekly subcutaneous administration of erythropoietin was effective for the treatment of renal anemia [11, 12, 13]. It is well known that younger children need relatively more erythropoietin than older ones [14] (*evidence*). Maintenance recommendations vary from 300 U/kg/week for a child with a weight of <20 kg to 120 U/kg/week for a child with a weight of >30 kg [10] (*opinion*). Each child will need the dosage titrated to achieve the target hemoglobin concentrations. For the titration of erythropoietin the DOQI guidelines can be used [2]. If the increase in hematocrit after initiation of erythropoietin therapy is less than 2% over a 2- to 4-week period, the dose should be increased by 50%. If the absolute rate of increase in hematocrit after initiation of erythropoietin therapy or after a dose increase exceeds 8% per month, the weekly dose of erythropoietin should be decreased by 25%.

Side effects of erythropoietin therapy are rare; increased clotting tendency, hypertension, and seizures are to be considered the consequence of the therapeutic effect rather than an adverse effect of the preparation. Nevertheless, blood pressure should be carefully monitored during therapy.

Recently, attention was drawn to a severe side effect of erythropoietin therapy, pure red blood cell aplasia due to the occurrence of neutralizing antierythropoietin antibodies [15, 16]. Subsequent investigations showed that this was in most cases associated with subcutaneously administered erythropoietin alpha from one brand, although some cases have also been described using the other brand available on the market. The application of erythropoietin beta is associated with a much lower incidence of this severe side effect. In many countries the subcutaneous administration of erythropoietin alpha is discouraged at present. The administration of darbepoetin alpha is not associated with pure red blood cell aplasia, but it should be remembered that experience with this drug is still limited.

Subcutaneous administration of drugs is psychologically distressing, especially for children (*opinion*). The use of ultrafine needles and special injection pens may help to alleviate the upset. In adult peritoneal dialysis patients a noncompliance with erythropoietin administration was reported in between 35% and 55% of patients [17, 18]. For children no data on erythropoietin are available, but from clinical practice it is known that subcutaneous administration is frightening and a source of conflict between child and caregivers. Limited data are available on the compliance with another drug which has to be administered subcutaneously, recombinant human

growth hormone. Noncompliance was reported to be between 50% and 91% [19, 20, 21]. In one study it was reported that noncompliance increased significantly from 41% at 1 year to 91% at 2 years [21]. Intravenous administration is a more expensive alternative, but will rarely be applied in pediatric peritoneal dialysis patients [22].

Despite some initial discouraging but still frequently cited reports in the literature, erythropoietin can be administered very well by the intraperitoneal route [23, 24]. If erythropoietin is administered in a small volume of dialysis fluid (50-ml bags are commercially available), bioavailability is similar to that after subcutaneous administration of the same amount of hormone [25] (*evidence*). Mean dosage needed for maintaining the target hematocrit decreased from 279 to 194 U/kg/week if the drug was administered in a 50-ml dialysis bag during the daytime [26, 27]. In a more recent study in 20 patients on nightly intermittent peritoneal dialysis mean dosage was 179 U/kg/week [28]. Dialysis adequacy is a major factor of concern in such a regimen: KT/V urea was ≥2.2 in the group studied. However, in some patients the application of intraperitoneal erythropoietin may be limited by the inability to obtain adequate dialysis (*opinion*). In patients not achieving adequate dialysis, the daytime period should be used for additional dialysis exchanges. In this category, that period will not be available for intraperitoneal erythropoietin therapy. Peritonitis frequency does not need to increase using intraperitoneal erythropoietin: the two pediatric studies reporting peritonitis rates mention one episode every 14.7 and 11.2 treatment months, respectively [19, 21]. One early study in children was broken off because of a high peritonitis rate [29]; possibly this was due to insufficient training of the caregivers.

Recently, an erythropoietin analogue was developed (darbepoetin alpha or NESP = novel erythropoiesis stimulating protein), which is a hyperglycosylated erythropoiesis-stimulating protein with a presumed threefold longer half-life than erythropoietin in man [30, 31, 32, 33, 34] (*evidence*). In children a two- to fourfold longer half-life was reported [35]. The pharmacokinetics when administered intravenously and subcutaneously appear to be the same in adult and pediatric patients. A randomized comparative study of darbepoetin and erythropoietin in pediatric patients with chronic or end-stage renal disease is just starting. There are no data available with respect to the intraperitoneal administration of darbepoetin.

The development of an orally active agonist of the erythropoietin receptor will be an interesting future feature [36].

Erythropoietin resistance may be due to a number of causes:

- Infection
- Hyperparathyroidism
- Malnutrition
- Hemolytic disorders
- Folate or vitamin B_{12} deficiency
- Underdialysis
- Vitamin C deficiency
- ACE inhibitors
- Anti-erythropoietin antibodies

Since there is an excellent review of these in the adult guidelines [2, 3, 37], and they are not essentially different in children, they are not discussed in detail here. In children responding poorly to erythropoietin therapy, special emphasis should be put on the possible contribution of inflammation or hyperparathyroidism [38]. The possible occurrence of pure red cell aplasia due to the development of neutralizing antierythropoietin antibodies has been discussed before.

Erythropoietin should be administered by the subcutaneous or intraperitoneal route in children on peritoneal dialysis (*evidence*). Although there is sufficient evidence to advocate the intraperitoneal administration of erythropoietin, most pediatric nephrologists still apply erythropoietin by the subcutaneous route in their peritoneal dialysis patients.

Iron

Iron supplementation is indicated in virtually all pediatric patients with renal anemia who are treated with erythropoietin. According to the DOQI guidelines, transferrin saturation should be maintained above 20% and serum ferritin concentration above 100 ng/ml [2] (*evidence*). There is no reason to anticipate that these guidelines should be different for children and for adults (*opinion*). It may be difficult to maintain sufficient iron stores in children on peritoneal dialysis, using oral iron preparations only. Iron supplements should be given to prevent iron deficiency and to maintain adequate iron stores. A dosage of 2–3 mg/kg body weight per day is recommended and administered in two to three divided doses either 1 or 2 h after food.

Iron supplements should not be added to the infant formula or nutrition supplements [39] (*evidence*). If possible, they should be prescribed with vitamin C to enhance absorption (*opinion*). However, it is important not to oversupplement with vitamin C for risk of increased oxalate formation. Iron supplements should ideally not be taken with cereals and legumes, tannins (tea, cocoa, chocolate) and dairy products as these interfere with absorption. Micronutrient supplements should also be prescribed following individualized dietary assessment and should account for the potential peritoneal dialysis losses of folic acid and vitamins C and B_6. Compliance with oral iron preparations for micronutrient supplements may be difficult and must be reinforced by both medical and dietetic staff [39, 40].

Parenteral iron preparations, commonly used in patients on hemodialysis, are more difficult to apply in children on peritoneal dialysis. After the recent approval of iron gluconate, iron sucrose, and iron saccharate, the application of iron dextran should also be abandoned in

the United States [41, 42, 43, 44] (*evidence*). Recommended dosage is 2 mg iron per kg per week for intravenous iron sucrose treatment [7]. Before starting intravenous therapy the administration of a test dosis is recommended. It is clear, however, that the intravenous administration of iron preparations is cumbersome, and oral administration is preferred [39] (*opinion*). In rare cases, for example with noncompliance with oral medication, intermittent intravenous administration will be indicated.

Limited but positive experience has been obtained with the intraperitoneal administration of iron dextran, both in rats and men [45, 46, 47]. Reports on the intraperitoneal administration of iron gluconate or iron sucrose are lacking.

Iron should preferably be prescribed as an oral preparation (*evidence*). In rare cases intermittent intravenous administration will be indicated.

Carnitine

Several studies in adult patients suggest that intravenous supplementation with L-carnitine reduces requirements for erythropoietin by 38–50% [48, 49, 50] (*opinion*). Published data on the effect of L-carnitine supplementation on the treatment of anemia in children are very scarce. One study showed an increase in the hematocrit by 34% in two children on hemodialysis with L-carnitine supplementation without modification of erythropoietin dosage [51]. Another study in 16 children on dialysis, of whom five were on peritoneal dialysis, showed no beneficial effect of oral supplementation with L-carnitine on erythropoietin requirement [52].

There is no precise place for carnitine supplementation in the treatment of anemia in pediatric peritoneal dialysis patients (*opinion*).

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