Devices for long-term hemodialysis in small children—a plea for action

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International registry data show that 11% to 37% of children initiating maintenance hemodialysis (HD) weigh less than 20 kg, with 4% to 14% weighing between 10 and 15 kg and 2% to 9% less than 10 kg.[1–3] The smaller blood volume in young children necessitates both low-volume tubing systems and dialyzers, and dialysis machines with a high precision of ultrafiltration control. The safe and tolerable extracorporeal blood volume in an individual is less than 8 ml/kg body weight, corresponding to 10% of the total blood volume.[4] If the extracorporeal volume exceeds this limit, circuit priming with human albumin or with packed red blood cells is recommended,[4] which could expose children to foreign proteins and blood from multiple donors, with an inherent risk of allergic reactions, blood-borne infections, and human leucocyte antigen sensitization.

HD equipment—requirements versus current availability

The technical prerequisites needed to safely perform long-term HD in small children are scarce. Currently available maintenance HD devices require an extracorporeal volume that is too high for children weighing below 10 kg and do not meet the stringent criteria for ultrafiltration accuracy that is critical for the smallest children. In children, an interdialytic weight gain of 4% is the upper safe limit that is not associated with left ventricular hypertrophy or vasculopathy. Removal of that fluid volume corresponds to an hourly ultrafiltration rate of approximately less than 10 ml/kg. However, according to the manufacturers, the ultrafiltration accuracy of many dialysis machines is rather rudimentary, varying from 20 to 50 ml per hour depending on the machine and dialysis modality (±1% of ultrafiltration ±0.1% of dialysate flow for the best described and precise machines). Excess ultrafiltration may lead, especially in the small infant, to rapid shifts in intravascular volume causing intradialytic hypotension and possible myocardial and cerebral ischemia. Inaccuracies in ultrafiltration control mandate that companies limit their

Countries	Weight (kg)					
	<10	10–<15	15–<20	20–<25	25–<30	30–<40
Australia	None	1	1	1	2	2
Canada	None	None	1	2	4	5
USA	None	None	1	2	3	5
European community	None	1	1	2	4	6
Japan	None	None	None	1	1	1

Figure 1 | Number of long-term hemodialysis machines approved for use in small children stratified by weight and geographic regions.

liability to a prespecified lower body weight limit, and, in turn, health regulatory agencies clear the devices only for use above these limits. Because of these major technical limitations, there is no device cleared for long-term HD in children weighing less than 10 kg anywhere in the world (Figure 1). In Europe and Australia, only 1 maintenance HD device is available and labeled for use in children weighing 10 to 20 kg, the Fresenius 6008 machine. In the USA and Canada, only 1 machine, the Baxter Phoenix X36, is cleared for use in children weighing 15 to 20 kg. In Japan, the Nikkiso DBB-200Si is cleared by the manufacturer for use in children weighing more than 20 kg (Figure 1). The Fresenius 5008 machine, a device that was cleared for HD in children above 10 kg and widely used, is no longer manufactured. Also, the newer continuous kidney replacement therapy devices that have been developed for infants cannot be used for long-term HD as the dialysate flow rate on these devices is too low.

Small children are denied the technological advances available to adults on HD

Several recent improvements in dialysis technology have ignored the needs for the youngest and most vulnerable patients. For example, hemodiafiltration can be performed in children >10 kg in Europe and Australia (with the Fresenius 6008 machine) but only in children >20 kg in Japan (with the Nikkiso DBB-200Si) and >40 kg in Canada (with the Fresenius 4008). Other recent advances including urea clearance monitoring, "real-time" blood volume controlled ultrafiltration and temperature control, evaluation of vascular access recirculation, and monitoring and control of sodium transfer during HD sessions[5] are either not built into HD machines that are approved for use in small children (as is the case for Baxter AK98), or if present, are only intended for use in patients >40 kg according to the manufacturers' instructions (as is the case for the Fresenius 6008).

Additional limitations exist with the latest machines from leading manufacturers that preclude single-needle dialysis in small children, either because the extracorporeal blood volume is too high: single-needle line volumes from 157 ml (Baxter AK98) to 231 ml (Nipro Surdial-X), or because single-needle treatment is not possible with the low-volume option required for children <40 kg (Fresenius 6008).

Access to approved, safe, and effective dialysis is a right for children

Children with kidney failure have a lifetime of kidney replacement therapy ahead of them.[6] They are at very high risk for cardiovascular complications, growth retardation, and cognitive impairment with a high symptom burden and poor quality of life, all of which are further aggravated by suboptimal dialysis.[6] Ethically, it is a *sine qua non* that children must have access to the same high-quality dialysis equipment available to adults on HD. The knowledge and technology are available to design the necessary equipment to successfully address this inequity.

What can we learn from Food and Drug Administration and the European Medicines Agency regulations on drugs?

As recently as 2 decades ago, children were effectively therapeutic "orphans," with huge gaps in pediatric labeling information and research. The US Food and Drug Administration and the European Medicines Agency responded to a call from pediatricians and the public on the lack of medicines that were appropriately tested for safety and efficacy in children of all ages. Collectively, the different drug development incentive legislations (United States Modernization Act [1997], Best Pharmaceuticals for Children Act [2002], Pediatric Research Equity Act [2003], Food and Drug Administration Safety and Innovation Act I [2012], and the European Union regulations [EU 1901/2006 and 1902/2006]) corrected the historical

legacy of inequity, with profoundly positive implications in terms of the care and outcomes for generations of children.

The same inequity of access exists for children who require medical devices for their treatment. Many children are being treated "off label" and are subject to interventions delivered by medical devices that lack pediatric safety and efficacy data. This is as unacceptable today as it was for children and access to drugs 25 years ago. The recent European Union regulation 2017/745 promises to increase the quality and safety of medical devices by demanding appropriate validation studies. Analysis of the 4-year transition period of this regulation reveals that it did not result in new and additional dialysis devices that are suitable for pediatric patients with kidney failure but rather is associated with progressive loss of the existing, mostly off-label use of the older machines. Although the basic technical requirements for HD are similar in children and adults, key aspects of the child's size, cardiovascular anatomy, and hemodynamic specifications demand pediatric-specific adaptations. This highly vulnerable patient group has largely been excluded from recent technical advancements, despite kidney replacement therapy being widely prescribed in otherwise stable children from the first days of life.[7]

There is an urgent need for a regulation on medical devices with sufficient incentives to solve this inequality, in parallel with what the regulation on orphan medicinal products (EC no. 141/2000) has achieved. On behalf of children who have kidney failure and who are receiving long-term HD, we plea for the same rights as afforded to adolescents and adults. There is an opportunity for regulators worldwide to require and even mandate device makers, especially of HD machines, to bring a symmetry of care for children that encompasses both drugs and medical devices. Safe and effective maintenance HD devices should not be restricted to adolescents and adults. The needs of newborns, infants, and small children on long-term HD must be considered from the earliest stages of a new HD device concept because postdesign adaptation to pediatric requirements has proven inadequate to date. Pediatric care providers, especially pediatric nephrologists, need to advocate for the support of regulatory agencies to mandate the development of high-quality equipment for their youngest patients. Similarly, society at large must demand the highest standards of technology to support this need for these vulnerable children.

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