Hypotension in Infants on Chronic Peritoneal Dialysis: Mechanisms, Complications, and Management

Enrico Vidal,1 Franz Schaefer2

Hypotension represents a very serious clinical problem in patients receiving renal replacement therapy, and it is associated with a significant increase in mortality risk. Infants on chronic peritoneal dialysis (CPD) can be particularly prone to chronic hypotension because of the hyponatremic hypovolemia risk related to their primary renal disease, their nutritional needs, and their peritoneal membrane characteristics. In this setting, if an acute clinical event leads to a further decline in systolic blood pressure, the counteract and perfusion pressure autoregulatory mechanisms can both be impaired, leading to severe complications.

Anterior ischemic optic neuropathy (AION) represents an acute ischemic disorder of the optic nerve head and a dramatic cause of sudden blindness, whose incidence is about 1% in children on CPD. In recent studies, very young age, autosomal recessive polycystic kidney disease, and sustained hypotension were found to be substantial risk factors for AION. In infants at risk, strategies of long-term treatment and prevention of peritoneal dialysis–induced hypotension should be applied to prevent progression in the pathophysiologic cascade that leads to chronic hypotension and its complications.

Key words
Children, hypotension, anterior ischemic optic neuropathy

Introduction
Dialysis-induced hypotension, the most frequent complication in patients treated with extracorporeal therapy, can occur in an episodic (intradialytic) or chronic (interdialytic) fashion. Information about the incidence, severity, and course of arterial hypotension in adults receiving chronic peritoneal dialysis (CPD) is limited.

The largest case series so far was described by Malliara et al. (1), who reported 81 hypotensive patients among 633 treated with CPD at 2 centers (Toronto, Ontario, Canada, and Thrace, Greece) between 1995 and 2000, for an incidence of 12.8%. In those hypotensive patients, mean age was 63.8 ± 14.2 years and median duration of CPD was 49.3 ± 30 months. Based on underlying pathophysiology, hypotension was caused in 39.5% of the patients by hypovolemia resulting from excessive ultrafiltration (UF) and excessive sodium loss because of the use of hyperosmolar dialysis solutions. Congestive heart failure was the cause in another 18.5%, and inadequate antihypertensive medication, in 13.6%. No cause could be identified in 28.4% of the patients. In comparing the 4 groups of hypotensive patients, no differences with respect to age, time on PD, relevant laboratory parameters, or dialysis adequacy were observed. During the study period, 53.1% of the hypotensive patients died, yielding an overall survival rate of 78% and 54% at 3 and 5 years respectively.

In patients on renal replacement therapy, blood pressure (BP) has been demonstrated to have a paradoxical association with clinical outcome. In a proportional hazards model, Goldfärb-Rumyantzev et al. (2) evaluated the association of systolic BP with all-cause mortality in a large sample of PD patients taken from the U.S. Renal Data System. The authors found that a systolic BP below 111 mmHg in PD patients was associated with a significantly higher mortality risk (hazard ratio: 2.71), and that a systolic BP above 120 mmHg was associated with fewer hospital days.
If hypotension in adults undergoing CPD is an under-discussed topic, then peritoneal dialysis (PD)–induced hypotension in infants is an almost unexplored area in the literature. The aim of the present review is to discuss risk factors, potential mechanisms, and prevention of PD-induced hypotension in children, and to report its complications, with particular regard to acute ischemic optic neuropathy (AION).

Discussion

**Hyponatremic hypovolemia-induced hypotension**

Infants on CPD are particularly prone to become salt-depleted. The subsequent decline in extracellular osmolality and loss of osmotic fluid into cells in turn leads to hypovolemia. The tendency toward sodium depletion in children on CPD is multifacto-ring and depends mainly on the specific primary cause of end-stage renal disease and on the peritoneal membrane characteristics.

Polyuric and salt-losing nephropathies account for nearly all cases of chronic renal failure in infants (3). Those diseases are characterized by impaired tubular function, leading to polyuria and sodium depletion as a consequence of either tubular immaturity (that is, renal dysplasia) or congenital or acquired tubular damage (that is, chronic interstitial nephritis and renal cystic disease). Urine output in affected children is typically 2 – 3 times normal, resulting in significant losses of free water and sodium. Attention to water and sodium replacement in this population is therefore important. According to the Italian Registry of Pediatric Chronic Dialysis, 11.3% of 291 pediatric CPD patients treated during 2000 – 2014 were already hypotensive at the start of renal replacement therapy (unpublished data).

The characteristics of the peritoneal membrane in infants on CPD can also explain the increased risk for hyponatremic hypovolemia. Measurements of the mass transfer area coefficient have suggested that, as a consequence of both higher peritoneal permeability and a larger effective surface area of peritoneal membrane, solute transport capacity is relatively greater in infants than in older children and adults (4). In these infants, sodium removal from plasma is, in addition to diffusion, mainly a consequence of UF-related convective transport (5). Compared with adults, infants with oliguria need a much higher UF rate per square unit of body surface area because their nutrition is based mainly on fluids. When UF rates are higher, approximately half the total UF depends on transport through the water-exclusive endothelial aquaporin 1 channels (ultrasmall pores); the remaining UF occurs through the small pores, leading to removal of sodium by solvent drag (6). During automated PD, about 8 mmol sodium are removed per 100 mL ultrafiltrate (7)—that is, in a 5-month-old anuric infant on CPD, 200 mL of daily UF is accompanied by the loss of about 16 mmol of sodium. International nutrition guidelines suggest that the sodium content of infant formula should be in the range 0.65 – 1.95 mmol/100 mL (8). If the same infant receives 500 mL of formula milk daily, sodium intake will be about 3 – 10 mmol. At normal serum sodium concentrations, sodium losses from UF are normally greater than the quantity ingested from infant formula, resulting in a tendency toward hyponatremia.

**Complications of PD-induced hypotension**

The thresholds of systolic BP define hypotension. According to the American Heart Association’s Pediatric Advanced Life Support guidelines, hypotension is defined as a systolic BP lower than 60 mmHg in term newborns (0 – 28 days), lower than 70 mmHg in infants (1 – 12 months), lower than 70 + (the child’s age in years × 2) mmHg in children 1 – 10 years, and lower than 90 mmHg in children more than 10 years of age. These BP thresholds are set just above the 5th percentile of systolic BP for age.

A fall of systolic BP in the systemic circulation results in increased sympathetic activity and catecholamine release, activation of the renin–angiotensin–aldosterone system, and vasopressin release, all of which stimulate the heart, blood flow, and volume redistribution. Thus, cardiac and central nervous system circulation are both maintained, and blood flow in cutaneous and splanchnic vessels is restricted. Despite fluctuations in arterial BP, perfusion of the central nervous system remains constant because of the mechanism of pressure autoregulation, a feature of the terminal arterioles that induces vasodilation during hypotension and vasoconstriction during hypertension (9). However, autoregulation operates only over a critical range of perfusion pressures (typically a mean BP on the order of 60 – 150 mmHg). With a rise or fall of perfusion pressure beyond the critical range, the mechanism becomes ineffective and breaks down. In chronically hypotensive CPD infants, a further drop in systemic BP caused by a “second hit” (excessive UF,
overestimation of an antihypertensive prescription, fever, vomiting, diarrhea, exaggerated nocturnal BP dipping) might impair the autoregulation of cerebral blood flow (Figure 1).

Posterior ciliary arteries are particularly vulnerable to a persistent drop in perfusion pressure, resulting in ischemic damage to the optic nerve head and peripapillary area (10). The clinical picture that arises is called nonarteritic AION, which represents a cause of sudden visual loss (11). In patients on CPD, AION is a rare complication, with a limited number of cases having been described in children (12–15). Very recently, Di Zasso et al. (16), on behalf of the Italian Registry of Pediatric Chronic Dialysis, described 7 children with AION among 721 pediatric patients treated with CPD over a 25-year period (1988 – 2013), corresponding to an incidence of about 1%. Interestingly, the registry included no reported cases of AION in children treated with HD during the same period. Mean age at AION onset in these children on CPD was 3.2 years, and of the 7 patients, 3 were described as chronically hypotensive. In the 4th child, a bilateral nephrectomy had been performed 3 months earlier for congenital nephrotic syndrome, and in the remaining 3 patients, inappropriate use of hyperosmolar PD solution and dehydration because of gastroenteritis were considered the probable triggers of hypotension. In most cases, the parents noted the visual loss at daylight after nocturnal sleep or after a nap during the day. The AION occurred after a median time on CPD of 13 months (range: 3 – 96 months). The 7 patients with AION were compared with age-matched children on CPD, and the authors confirmed a significantly lower systolic BP in the cases (standard deviation score: –2.25) than in the controls (standard deviation score: +1.18; \( p < 0.001 \)).

Dufek et al. (17) scrutinized 14 children on CPD presenting with AION and compared them with a control cohort of 59 non-affected patients to identify a risk profile for AION. Very young age at CPD initiation, autosomal recessive polycystic kidney disease as the primary cause of end-stage renal failure, anephric status, and chronic hypotension were found to be significant risk factors for AION. In this case series, 5 patients had a “good” visual outcome (visual acuity still quantifiable according to Snellen charts), but 9 children remained blind. The outcome of AION seemed to be closely related to an aggressive vascular refilling therapy. All patients with a “good” outcome and only 1 of the 9 with a poor outcome received fluid boluses within 12 hours after the onset of symptoms. Intravenous steroids to reduce optic nerve inflammation and disk edema did not improve the outcome of AION in children on CPD.

**Prevention of PD-induced hypotension**

Strategies for the long-term treatment and prevention of PD-induced hypotension should be used to prevent progression in the pathophysiologic cascade that leads to chronic hypotension. To avoid chronic intravascular depletion and to promote optimal growth, infants and

![Proposed pathophysiologic sequence of events involved in determining peritoneal dialysis–induced hypotension and its complications. BP = blood pressure; AION = anterior ischemic optic neuropathy.](image)
children with polyuric salt-wasting forms of chronic kidney disease should receive sodium supplements (18). Individualized therapy can be accomplished by first prescribing at least the age-related Dietary Reference Intakes for sodium, even if better linear growth outcomes were reported in infants with chronic kidney disease who received a 2 – 4 mmol/L dose of sodium in infant formula (19).

Even when anuric, infants on CPD are predisposed to substantial sodium losses as a result of high UF requirements. Sodium balance measurements (determined from dietary and medication intake and dialysate effluent losses) are therefore suggested at least every 6 months, concurrent with measurement of dialysis adequacy (18). A higher sodium concentration in the dialysate (137 – 138 mmol/L) might be required to prevent excessive sodium losses from the convective transport via transcapillary UF. If urine output is still preserved in these infants, supplemental sodium (as much as 5 – 10 mEq/kg) might also be necessary because of the combined sodium losses in urine and dialysate (20).

Prevention strategies should also be applied to avoid clinical events that could induce a further decline in blood perfusion pressure, which in turn potentially leads to a failure of autoregulation. In young infants, accurate calculation and frequent assessment of “dry weight” to avoid excessive use of hyperosmolar PD solutions should be performed. In this setting, the new concept of adapted automated PD as suggested by Fischbach et al. (21) might be convenient. Their method uses a short dwell time with a small fill volume to promote UF only in the first dialysis cycles; subsequent cycles use a longer dwell time and a larger fill volume to promote removal of uremic toxins.

In infants receiving CPD, meticulous attention should be paid to all causes that can potentially lead to an alteration in the volume of circulating blood. Hypovolemia can be absolute (for example, because of dehydration from severe diarrhea and vomiting) or relative. The latter condition is also called “distributive hypovolemia” and can occur with an increase in the volume of the intravascular space—for example, during a febrile event, or after exaggerated or inappropriate prescription of antihypertensive medications. In cases of acute gastroenteritis, children treated with CPD should be carefully evaluated with respect to opportunities to initiate intravenous rehydration and to modify the dialysis prescription (reduced treatment time, increased dwell time, minimized dialysate glucose content). In an acute febrile event, discontinuation of antihypertensive medication should also be considered.

Summary
Hypotension represents an adverse phenomenon in infants receiving CPD. In small children, fluid and electrolyte supplementation, nutritional requirements, and the dialysis prescription should be carefully monitored to prevent the onset of this complication. When dealing with infants receiving CPD, prevention of severe hypotensive events is of utmost importance because of the associated risk for nonarteritic AION, a potentially blinding disease.

Disclosures
EV and FS have no personal financial disclosures to report.

References

Corresponding author: Enrico Vidal, MD, Nephrology, Dialysis and Transplant Unit, Department of Women’s and Children’s Health, University-Hospital of Padova, 3 Via Giustiniani, Padova 35128 Italy.
E-mail: enrico.vidal@inwind.it