

# Interdialytic weight gain in oligoanuric children and adolescents on chronic hemodialysis

Fabio Paglialonga · Silvia Consolo · Maria Albina Galli · Sara Testa · Alberto Edefonti

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## Abstract

**Background** Little is known about the clinical impact of interdialytic weight gain (IDWG) on oligoanuric children undergoing chronic hemodialysis (HD).

**Methods** We retrospectively assessed IDWG, left ventricular mass index (LVMI) and its changes ( $\Delta$ LVMI), pre-HD systolic and diastolic blood pressure (DBP), residual urine output, Kt/V, the frequency of intradialytic symptoms, normalized protein catabolic rate, and the 3-month change in the dry weight of 16 hemodialyzed oligoanuric patients with a median age of 14.8 years (range 5.0–17.9).

**Results** There was a significant correlation between IDWG and median LVMI ( $r$  0.55,  $p=0.026$ ), which was  $27.3 \text{ g/m}^{2.7}$  (22.5–37.6) in the patients with a median IDWG of  $<4\%$ , and  $44.3 \text{ g/m}^{2.7}$  (28.2–68.7) in those with a median IDWG of  $>4\%$  ( $p=0.003$ ). None of the four patients with an IDWG of  $<4\%$  showed left ventricular hypertrophy, compared with 10 of the 12 patients (83.3 %) with an IDWG of  $>4\%$  ( $p=0.003$ ); the former also had a better median  $\Delta$ LVMI ( $-33.5\%$  vs  $-13.0\%$ ;  $p=0.02$ ) and a lower median DBP sds (0.24 vs 1.72,  $p=0.04$ ).

**Conclusions** There is a significant correlation between IDWG and LVMI in pediatric oligoanuric patients on chronic HD: those with an IDWG of  $>4\%$  are at a higher risk of left ventricular hypertrophy.

**Keywords** Interdialytic weight gain · Pediatric hemodialysis · Left ventricular mass index · Left ventricular hypertrophy · Dry weight

F. Paglialonga (✉) · S. Consolo · S. Testa · A. Edefonti  
Pediatric Nephrology and Dialysis Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via Commenda 9,  
20122 Milan, Italy  
e-mail: fabiopaglialonga@alice.it

M. A. Galli  
Pediatric Cardiology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

## Introduction

Cardiovascular disease is a major cause of morbidity and mortality among patients with end-stage renal disease (ESRD), and left ventricular hypertrophy (LVH) is a frequent complication affecting children and adults on chronic dialysis [1–6]. The possible factors predisposing pediatric ESRD patients to LVH include hypertension, a high body mass index, primary renal diseases other than hypodysplasia, anemia and hyperparathyroidism, and hemodialysis (HD) as a dialysis modality [6–11]. A number of studies of adults undergoing HD have suggested that volume overload might play a role in determining LVH, but there are no published pediatric data in this regard [12–14].

Any comprehensive approach to the problem of volume overload in ESRD patients includes the assessment of dry weight (DW) and the control of interdialytic weight gain (IDWG). Assessing DW is of particular concern in the pediatric population because of the absence of a known gold standard of body composition and, although intradialytic blood volume monitoring and bioimpedance analysis seem to be promising, there is still little evidence supporting their use [15–21]. Interestingly, a better DW assessment could lead to a significant improvement in left ventricular mass index (LVMI), not only in adults but also in children on HD [13, 21]. IDWG is a key factor in the management of patients on chronic HD for various reasons: first of all, a high IDWG leads to a supra-physiological expansion of extracellular water and consequent volume overload; second, excessive ultrafiltration during HD carries the risk of relative hypovolemia and myocardial stunning, with their possibly serious negative effects on cardiac status [22]; and third, patients with a persistently high IDWG may fail to reach the desired DW and thus remain in a state of chronic overload. All of these mechanisms can lead to a progressive increase in left ventricular mass and chronic cardiovascular sequelae [23, 24], but little is known about the clinical impact of IDWG on children on chronic HD.

The aim of this study was to assess the relationship between IDWG and cardiovascular status in chronically hemodialyzed oligoanuric children and adolescents.

### Patients and methods

This retrospective study involved all of the oligoanuric patients (daily urine output  $\leq 0.5$  mL/kg/h) aged 3–18 years who underwent chronic thrice-weekly HD in our pediatric unit between 1 January 2012 and 31 August 2013, who had been clinically stable during HD for more than 3 months, who had undergone echocardiography twice within a period of no more than 6 months, and who had no intercurrent diseases or clinical instability at the time of echocardiography.

The median IDWG of each patient (defined as the difference between current pre-HD body weight and estimated DW) during the month preceding the last echocardiogram was calculated as a percentage of estimated DW. Our assessment of DW was largely based on the use of bioimpedance analysis, as previously described: a range of patient-specific reactance values was identified at which each child could be considered as being at DW on the basis of complex multidisciplinary criteria (intra- and interdialysis clinical symptoms, blood pressure, biochemical indices, blood volume monitoring, echocardiography) [21]. Values that were lower than the patient-specific limit suggested the need for a reduction in DW, whereas higher values (accompanied by clinical symptoms of hypovolemia such as cramps and hypotension) suggested that DW should be increased [21].

The following parameters were also retrospectively assessed and their correlations with IDWG were analyzed:

1. Left ventricular mass index (LVMI) was calculated on the basis of LVM as measured by means of two-dimensional M-mode echocardiography at the end of the HD session (usually at least 1 h after the end of the session) using the formula of the American Society of Echocardiography, divided by height raised to a power of 2.7: LVH was defined as an LVMI of  $>38$  g/m<sup>2.7</sup> [25, 26]. All of the echocardiographic examinations were performed by the same three pediatric cardiologists.
2. The percentage change in LVMI from the time of a previous echocardiographic examination carried out no more than 6 months earlier.
3. The percentage of symptomatic dialysis sessions (i.e., those complicated by the occurrence of cramps, headache, abdominal pain or hypotension requiring medical intervention) in the month preceding echocardiography.
4. Median predialysis systolic and diastolic blood pressure (SBP and DBP) during the month preceding echocardiography, expressed as standard deviation scores (sds). Blood pressure at rest was routinely measured by renal

nurses using a calibrated oscillometric device and cuff sizes appropriate for children. The mean of three consecutive determinations was recorded.

5. The percentage change in DW during the 3 months preceding echocardiography, calculated as:

$$(\text{DW at the time of echocardiography} - \text{previous DW}) / \text{previous DW}$$

where previous DW is the DW established 3 months before the echocardiographic study.

6. Residual urine output (mL/kg/day).
7. The number of antihypertensive medications, in particular angiotensin-converting enzyme (ACE) inhibitors.
8. Dialysis adequacy assessed on the basis of single-pool Kt/V (spKt/V) and equilibrated Kt/V. Single-pool Kt/V was calculated using the formula

$$\text{spKt/V} = -\ln[(C_t/C_0) - 0.008 * t] \\ + [4 - 3, 5 * (C_t/C_0)] * \Delta \text{BW} / \text{BW}$$

where  $C_0$  = BUN (mg/dL) at the beginning of the HD session,  $C_t$  = BUN at the end of the session,  $t$  = treatment time (h),  $\Delta \text{BW}$  = body weight loss (kg), and  $\text{BW}$  = predialysis body weight (kg).

Equilibrated Kt/V (eKt/V) was calculated on the basis of spKt/V and dialysis time as follows:

$$\text{eKt/V} = \text{spKt/V} - (0.6 * \text{spKt/V} / t) + 0.03$$

9. Normalized protein catabolic rate (nPCR), calculated using a modified version of Borah's equation:

$$\text{nPCR} = 5.43 \times G / \text{V1} + 0.17$$

where  $\text{V1}$  is post-dialysis total body water (L) ( $=0.58 \times \text{BW}$  in kg), and  $G$  the urea generation rate, which can be calculated as follows:

$$G \text{ (mg/min)} : [(C_2 \times \text{V2}) - (C_1 \times \text{V1})] / t$$

where  $C_1$  = post-dialysis BUN,  $C_2$  = pre-dialysis BUN,  $\text{V1}$  = post-dialysis total body water (dL:  $5.8$  dL/kg  $\times$  post-dialysis weight in kg),  $\text{V2}$  = pre-dialysis total body water (dL:  $5.8$  dL/kg  $\times$  post-dialysis weight in kg), and  $t$  = time (min) from the end of one dialysis treatment to the beginning of the next.

10. The following laboratory parameters measured at the beginning of a mid-week dialysis session in the month

preceding echocardiography: hemoglobin, potassium, phosphate, and parathyroid hormone (PTH).

No significant changes in dialysis staff were made during the study period. Dialysate sodium was 138 mEq/L for all patients, and the maximum hourly ultrafiltration allowed during a single session was individualized, but did not exceed 20 mL/kg/h. Dialysis duration was 3.5 or 4 h in all the patients. The policy in our Unit to optimize ultrafiltration in the case of excessive IDWG was to increase the dialysis time by half an hour; no ultrafiltration profile was routinely used. Rescue sessions were planned only in the event of it being impossible to reach the target dry weight before the long interdialytic interval.

Data were expressed as median values and ranges, and were statistically analyzed using the Mann–Whitney test for continuous variables and Fisher’s exact test for dichotomous variables. Linear and logarithmic regression and Pearson’s correlation coefficient were used to assess the correlations between the study parameters. The Stat-View software (SAS Institute) was used for the statistical analysis. A *p* value of <0.05 was considered statistically significant.

**Results**

The study involved 16 children and adolescents (8 girls, 8 boys) with a median age of 14.8 years (range 5.0–17.9). Their characteristics are summarized in Table 1.

The median IDWG was 5.1 % (range 2.2–7.4 %) as a percentage of body weight and 1.65 kg/session/patient as an

absolute value (range 0.58–4.2 kg); the median LVMI was 27.3 g/m<sup>2.7</sup> (22.5–68.7).

A significant correlation was found between IDWG and LVMI (*r* 0.55, *p* = 0.026). According to a logarithmic regression model, IDWG was also slightly correlated with SBP sds (*r* 0.19, *p* = 0.10) and significantly correlated with DBP sds (*r* = 0.56, *p* = 0.03). The regression lines between IDWG and the above-mentioned cardiovascular parameters are shown in Fig. 1. There were no significant correlations between IDWG and the other study parameters.

The LVMI was also significantly correlated with SBP sds (*r* 0.83, *p* = 0.0001) and DBP sds (*r* = 0.62, *p* = 0.01); no significant associations were observed between LVMI and the other study parameters, including laboratory tests, residual renal function, vascular access, and use of antihypertensives.

Ten of the 16 patients (62.5 %) had some degree of LVH. Only 4 out of 16 (25 %) showed a median IDWG of <4 % of body weight, none of whom had LVH. The prevalence of LVH was 83.3 % (10 out of 12) in the patients with an IDWG of >4 % (*p* = 0.003). Using the conventional IDWG cut-off point of 5 %, LVH was diagnosed in 3 out of 7 children with an IDWG of <5 % (42.8 %) and 7 out of 9 patients with an IDWG of >5 % (77.8 %, *p* = 0.15).

As shown in Table 2, the patients with a mean IDWG of <4 % of body weight had significantly lower LVMI and DBP values, and tended to have lower SBP. The reduction in LVMI between the previous and last echocardiographic examination was also significantly better in the patients with an IDWG of <4 %. There were no significant between-group differences in terms of the incidence of symptomatic sessions, residual urine output, use of antihypertensives (in particular ACE inhibitors), vascular access, biochemistry, the parameters of HD adequacy, nPCR or changes in DW over the previous 3 months.

The median urine output was 3 mL/kg/day (0–12); no patients had a residual urine output >250 mL/day. Seven of the 16 patients were completely anuric: the IDWG in this group was 5.4 % (range 4.6–7.4 %), not significantly different from the 5.2 % (2.2–6.9 %; *p* = 0.64) observed in the patients with a partially preserved urine output. The same was true for median LVMI, which was 41.6 g/m<sup>2.7</sup> (28.2–61.3) in the anuric group, and 42.1 g/m<sup>2.7</sup> (22.5–68.7) in the non-anuric group (*p* = 0.64).

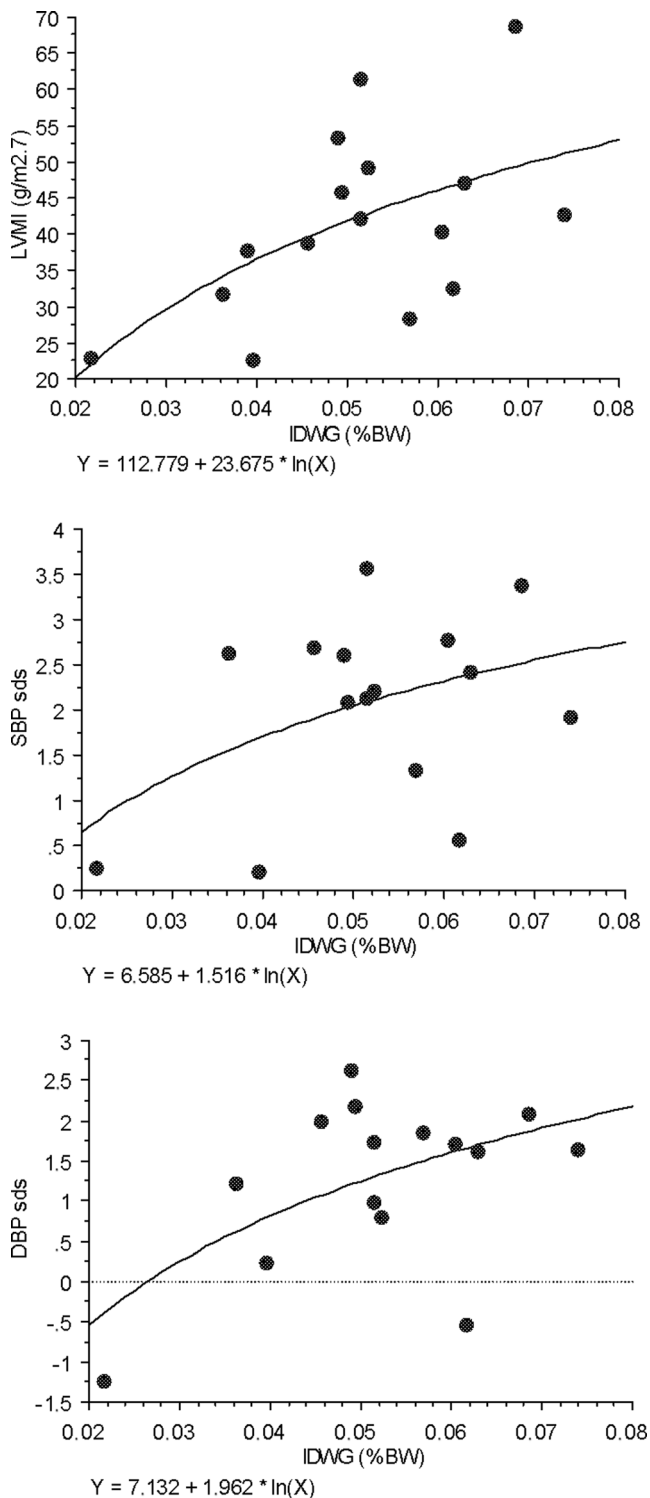
**Discussion**

Advances in the management of children on dialysis notwithstanding, cardiovascular disease remains a leading cause of hospitalization and death [1]. It is widely acknowledged that LVH is a common complication of uremia, and accepted that it can be used as a surrogate end-point to evaluate cardiac impairment in dialyzed children [2–6].

**Table 1** Patient characteristics at the beginning of the study

Characteristic	Data
Number of patients	16
Gender (male/female)	8/8
Median age, years (range)	14.8 (5.0–17.9)
Median age at start of dialysis, years (range)	12.4 (1.1–16.6)
Median duration of dialysis, years (range)	1.7 (0.4–6.7)
Vascular access (AVF/CVC)	13/3
Estimated median dry body weight, kg (range)	36.8 (19–60.1)
Primary kidney disease	
FSGS	4
Nephronophthisis	3
Glomerular diseases	3
Renal dysplasia	2
Hemolytic uremic syndrome	2
Others	2

AVF arteriovenous fistula, CVC central venous catheter, FSGS focal segmental glomerulosclerosis



**Fig. 1** Logarithmic regression lines between interdialytic weight gain (IDWG) as a percentage of body weight (BW) and left ventricular mass index (LVMI), and the standard deviation scores of systolic blood pressure (SBP) and diastolic blood pressure (DBP)

Among the various factors potentially leading to LVH, volume overload has received increasing attention over the last few years. Some studies of adults on chronic HD have

shown that better adjustment of DW obtained by intensifying ultrafiltration can reduce left ventricular mass, and the findings of a recent study of pediatric patients on HD suggest that a more precise assessment of DW based on bioimpedance analysis might be associated with a reduced incidence of pulmonary edema and an improved LVMI [21].

The results of the present study highlight a significant correlation between IDWG and LVMI, and show that patients with a high IDWG are at a greater risk of LVH. Similar to what has been shown in adults [12–14], we also found that patients with a high IDWG tended to have higher BP levels than those with a low IDWG; however, these findings must be interpreted cautiously, given that pre-dialysis blood pressure is a poor index of overall blood pressure in HD patients. Twenty-four-hour ambulatory blood pressure monitoring (ABPM) is known to better predict cardiovascular morbidity than casual blood pressure measurement; unfortunately, ABPM data were not available in our study [27].

The design of the study does not make it possible to demonstrate a causal relationship between the study parameters, but various mechanisms can be hypothesized to explain these findings. The most obvious are severe pre-HD volume overload and chronic volume overload due to a recurrent failure to reach the targeted DW, but other potential mechanisms linking IDWG and LVH include myocardial stunning, which can occur more often in the case of a high ultrafiltration rate [22].

It obviously cannot be excluded that IDWG and cardiovascular parameters may be simply covariates without any causal relationship between them. It can be hypothesized that IDWG and LVMI might both be influenced by residual renal function, and that the cardiac impairment might be due to an impairment in the renal clearance of uremic toxins; however, we only included oligoanuric patients. Moreover, although we did not systematically assess residual renal clearance, no differences in IDWG or LVMI were observed between the completely anuric patients and those with a partially preserved urine output. A further hypothesis is that patients who fail to comply with their limited prescribed fluid intake may also be less compliant with drug therapy, particularly to anti-hypertensive medications. Although the lack of differences in biochemical data between patients with high IDWG and low IDWG does not seem to support the hypothesis of non-compliance to drugs in patients with excessive fluid intake, the absence of ABPM data makes it impossible to draw definitive conclusions about overall blood pressure control [27].

It is interesting that we did not observe a higher incidence of symptomatic sessions in the patients with a higher IDWG: patients who require considerable fluid removal during dialysis are in any case at a high risk of cardiovascular complications, even though they seem to tolerate very high ultrafiltration rates well. The negative impact of excessive IDWG and a high ultrafiltration rate on the outcome of patients on



**Table 2** Comparison of patients with an interdialytic weight gain (IDWG) <4 and >4 % (median values and ranges)

	IDWG <4 % (4 patients)	IDWG >4 % (12 patients)	<i>p</i>
Age, years	14.9 (5.0–16.8)	14.4 (5.4–17.9)	0.81
Age at start of dialysis, years	13.2 (3.9–14.3)	11.8 (1.1–16.6)	0.81
Duration of dialysis, years	2.1 (1.0–2.6)	1.4 (0.4–6.7)	0.90
Ultrafiltration/session, % BW	3.6 (2.2–3.9)	5.5 (4.6–7.4)	0.0009
LVMI, g/m <sup>2.7</sup>	27.4 (22.5–37.6)	44.3 (28.3–68.7)	0.003
LVH (%)	0/4 (0 %)	10/12 (83.3 %)	0.003
Delta LVMI, %	−33.5 (−37 / −23)	−13.0 (−39.3/+28.6)	0.02
SBP, sds	0.24 (0.2–2.6)	2.3 (0.6–3.6)	0.14
DBP, sds	0.24 (−1.2–1.2)	1.72 (−0.5–2.6)	0.04
Symptomatic sessions, %	0 (0–7.7)	7.7 (0–15.4)	0.30
Number of antihypertensive drugs/patient	3 (2–4)	2 (0–4)	0.39
Number of patients on ACE inhibitors (%)	2/4 (50 %)	7/12 (58.3 %)	0.90
SpKt/V	1.49 (1.2–1.8)	1.46 (1.1–1.9)	0.9
eKt/V	1.30 (1.0–1.6)	1.27 (1.0–1.7)	0.9
nPCR, g/kg/day	1.29 (1.1–1.7)	1.43 (0.8–2.9)	0.40
Weight gain in 3 months, %BW	0.5 (0–5.6)	2.7 (−5.1–+8.3)	0.63
Hemoglobin, g/dL	11.2 (10.7–11.8)	11.4 (9.8–13.5)	0.94
Potassium, mEq/l	5.4 (5.2–5.5)	5.7 (3.7–7)	0.39
Phosphate, mg/dL	5.5 (4.4–6.1)	5.4 (2.5–9.5)	0.77
PTH, pg/mL	581 (406–651)	231 (108–1,306)	0.47
Number of anuric patients (%)	1 / 4 (25 %)	6/12 (50 %)	0.37
Urine output, mL/kg/day	9 (0–12)	4 (0–12)	0.76

*BW* body weight, *LVMI* left ventricular mass index, *LVH* left ventricular hypertrophy, *SBP* systolic blood pressure, *sds* standard deviation score, *DBP* diastolic blood pressure, *nPCR* normalized protein catabolic rate, *PTH* parathyroid hormone

hemodialysis is not new, if the adult literature is considered: in adult patients on HD an excessive ultrafiltration rate is independently associated with an increased long-term risk of death [23].

The last important study finding is the lack of a correlation between IDWG and nutritional parameters, particularly nPCR and the 3-month increase in body weight. These two indices may not be the best nutritional parameters, but the data do not support the view that greater fluid intake during the interdialytic period is associated with a higher calorie and protein intake. Conversely, the negative possible impact of hypervolemia on nutritional status must be considered, given that an association between protein-energy wasting and volume overload has been described, mainly in adults [23].

It is necessary to consider some limitations when interpreting the findings of the study: its retrospective design does not exclude the possibility that the results may have been affected by some biases, and the study population was small. However, it is worth remembering that it was very homogeneous as all of the patients were oligoanuric, and the fact that they underwent thrice-weekly HD at a single center over a short period of time ensured that they were similarly managed. Some methodological flaws must also be taken into account, such as the lack of ABPM data, which could have helped in

better understanding the relationship among IDWG, blood pressure, and left ventricular mass [27].

Despite these limitations, this is to our knowledge the first pediatric study to highlight a significant correlation between IDWG and cardiovascular parameters, and the findings indicate that there is a need for new strategies aimed at counteracting the problem of volume overload in children on HD. Intensive patient and family education should be the first approach, but, as non-compliance is very common, particularly in adolescents, it may not be enough in clinical practice, and it is necessary to take into account the possible detrimental effects of a too restricted diet on the patient's nutritional status and quality of life. On the basis of findings in adults, it may be useful to reduce dialysate sodium levels: although dialysate sodium was low or normal in our patients (138 mEq/L), the high inter- and intraindividual variability of plasma sodium levels in children on HD lets us imagine that the mean prescribed dialysate sodium was in some cases higher than the predialytic plasma sodium. An individualized dialysate sodium prescription could actually optimize diffusive sodium removal during HD, but it is difficult to achieve in clinical practice [28]. The optimal approach to the problem of excess IDWG is probably an intensified dialysis regimen as there is a considerable amount of adult data indicating that daily or nocturnal HD is associated with a

dramatic improvement in the cardiovascular status of patients with ESRD, and pediatric experience points in the same direction [29–35]. Fischbach et al. converted five oligoanuric children from standard on-line hemodiafiltration to daily on-line in-center hemodiafiltration, and obtained a significant decrease in arterial blood pressure and LVMI, and Goldstein et al. observed a progressive reduction in casual pre-treatment SBP and DBP, the discontinuation of antihypertensive medications, and a decrease in ambulatory monitored BP after switching four children from conventional thrice-weekly HD to six sessions of home HD a week [31, 32]. Furthermore, the benefits of intensified HD regimens are not limited to cardiovascular status, but also include improvements in other outcomes such as metabolic control, growth, nutritional intake, post-HD recovery times, and school attendance [29–35].

In conclusion, our findings show a significant correlation between IDWG and LVMI in children and adolescents undergoing chronic HD, and patients with high levels of IDWG are at a high risk of LVH. Further studies are needed to confirm these findings and to identify optimal treatment strategies, particularly the benefits of intensified HD regimens.

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