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Prescribing peritoneal dialysis for high-quality care in children

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Summary statements

- We suggest initiating dialysis in children at an estimated glomerular filtration rate of <10 ml/ml/1.73 m^2 or when the child with chronic kidney disease has uremic symptoms refractory to medication and/or dietary management **(grade 2D)**.
- In children, selection of the dialysis modality should be based on the parents/caregivers' choice, child's age and size, presence of comorbidities, family support available, modality contraindications, and expertise of the dialysis team and the child. Preserving dialysis access, both peritoneal and vascular access, must be considered when selecting the optimal dialysis modality for a child **(ungraded)**.
- We suggest assessing the patient's dry weight at each clinic visit with clinical evaluation, including the measurement of weight and blood pressure, laboratory parameters and objective measurements of fluid status using bioimpedance spectroscopy, where available, in order to help guide the peritoneal dialysis (PD) prescription and ultrafiltration requirements **(grade 2C)**.
- We suggest that euvolemia and normotension be achieved in the child on PD through:
  (i) dietary sodium and fluid restriction;
  (ii) promoting residual diuresis and use of renin–angiotensin aldosterone system (RAAS) inhibitors (with appropriate monitoring for hyperkalemia and temporary discontinuation during episodes of dehydration); and
  (iii) use of icodextrin to enhance ultrafiltration **(grade 2D)**.
- We suggest that the PD prescription should be adjusted with the goal of achieving a normal serum phosphate level. A total minimum weekly urea clearance (Kt/Vurea) of 1.7 should be targeted in children on PD, with modifications based on regular assessment of clinical well-being and laboratory parameters, if required **(grade 2D)**.

Abstract

Background: Peritoneal dialysis (PD) remains the most widely used modality for chronic dialysis in children, particularly in younger children and in lower and middle income countries (LMICs). We present guidelines for dialysis initiation, modality selection, small solute clearance, and fluid removal in children on PD. A review of the literature and key studies that support these statements are presented.

Methods: An extensive Medline search for all publications on PD in children was performed using predefined search criteria.

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Results: High-quality randomized trials in children are scarce and current clinical practice largely relies on data extrapolated from adult studies or drawn from observational cohort studies in children. The evidence and strength of the recommendation is GRADE-ed, but in the absence of high-quality evidence, the opinion of the authors is provided and must be carefully considered by the treating physician, and adapted to local expertise and individual patient needs as appropriate. We discuss the timing of dialysis initiation, factors to be considered when selecting a dialysis modality, the assessment and management of volume status on PD, achieving optimal small solute clearance, and the importance of preserving residual kidney function. While optimal dialysis must remain the goal for every patient, a careful discussion with fully informed patients and caregivers is important to understand the patient and family's expectations of dialysis and reasonable adjustments to the dialysis program may be considered in accordance with a philosophy of shared decision-making.

Conclusions: There continues to be very poor evidence in the field of chronic PD in children and these recommendations can at best serve to guide clinical decision-making. In LMICs, every effort should be made to conform to the framework of these statements, taking into account resource limitations.

Keywords
Peritoneal dialysis (PD), adequacy, children, fluid overload, hydration, phosphate, quality of life

Literature review

Medline was searched using the PubMed interface through October 1, 2018 (no start date), using search terms and strategies detailed relevant to these guidelines. Limits were preset to manuscripts published in the English language.

Studies included

The following types of studies were included:

- all systematic reviews and randomized controlled trials in children on chronic peritoneal dialysis (PD) (none available);
- all prospective observational studies in children (irrespective of number of patients or duration of study) on chronic PD;
- retrospective studies in children on chronic PD (if >20 children included);
- data from international registries describing outcomes in children on chronic PD. Data from prospective studies with <20 children and from retrospective studies and registries have been included in the evidence review, but the evidence is taken with caution and the study quality downgraded.

Studies excluded

- Studies of persons >18 years of age;
- Studies of patients on acute PD, defined as PD for $\leq$3 months.

Stakeholder feedback

A final draft of the manuscript was circulated to patients and their caregivers as well as dialysis nurses across all centers. Their feedback has been incorporated into the document.

Dialysis initiation

We suggest initiating dialysis in children at an estimated glomerular filtration rate (eGFR) of <10 ml/ml/1.73 m^2 or when the child with chronic kidney disease (CKD) has uremic symptoms refractory to medication and/or dietary management.

Level of evidence—Grade 2D

Rationale. The timing of dialysis initiation is a complex decision that should be taken into account the eGFR as well as signs and symptoms of uremia that include:

- inability to maintain euvolemia with the development of hypertension and/or significant peripheral edema;
- deterioration in nutritional status or growth failure and declining weight and/or height centiles;
- biochemical abnormalities such as hyperkalemia, hyperphosphatemia, or acidosis; and
- subjective complaints of the patient, including loss of appetite, nausea, fatigue, inability to concentrate, and perceived poor quality of life.

Before dialysis is undertaken, these conditions should be shown to be persistent and refractory to medication and/or dietary management. The duration of uremic symptoms before dialysis deemed necessary will depend on their severity as well as the distress they are causing the child. The decision to start dialysis should be reached as part of a discussion between the child (if age appropriate), their caregivers, and their health-care providers.

In children, the percentage of patients who initiated dialysis in the United States with an eGFR >10 ml/min/1.73

m^2 has increased from 16.5% in 1995 to 40.8% in 2015. In a recent analysis of United States Renal Data System (USRDS) data from a total of 15,473 children, who were initiated on dialysis between 1995 and 2015, 29% (4481) were started when the eGFR was >10 ml/min/1.73 m^2 (median 12.8 ml/min/1.73 m^2).[1] Compared to the patients who initiated dialysis with an eGFR <10 ml/min/1.73 m^2 (median eGFR 6.5 ml/min/1.73 m^2), the risk of death (censored at kidney transplant) was 24% higher for those who started on dialysis at a higher eGFR. However, when dialysis modality was taken into consideration, the increased risk of mortality associated with "early" dialysis initiation did not reach statistical significance for the PD population ($n = 6148$).[1] A recent registry report from the European Society of Pediatric Nephrology/European Renal Association-European Dialysis and Transplant Association Registry examined dialysis initiation in 2963 children from 21 countries.[2] There were no clinically relevant benefits noted among those who started dialysis at an eGFR more than or less than 8 mL/min/1.73 m^2 in terms of survival, growth, or access to transplantation; however, hypertension was more prevalent among late initiators.[2] While these studies are registry reports only and must be interpreted with caution, the accuracy of eGFR estimation in late stages of CKD must also be interpreted with caution.[3]

The Schwartz bedside formula, which can be used to estimate GFR in children, was developed in the CKD in children study and is most valid in the GFR range of 15–75 ml/min/1.73 m^2 and with the use of standardized serum creatinine methods traceable to the isotope dilution mass spectrometry technique.[2] In the setting when a creatinine-based estimate may be inaccurate (e.g. patient with poor muscle mass) and there is no good agreement between the Schwartz bedside formula and a univariate cystatin C-based formula, a measured GFR, if available, may be useful. In both pediatric and adult patients, estimating equations based on both serum creatinine and cystatin C values provide a better estimate than equations based on either biomarker alone.[4,5]

Modality selection

In children, selection of the dialysis modality should be based on the child's age and size, presence of comorbidities, family support available, modality contraindications, expertise of the dialysis team, and the child and parents/caregivers' choice. Preserving dialysis access, both peritoneal and vascular access, must be considered when selecting the optimal dialysis modality for a child.

Level of evidence—Ungraded

Rationale. There are no studies to suggest that either PD or hemodialysis (HD) is superior in children with end-stage kidney disease (ESKD).[6] International registries suggest that PD is the preferred and most widely used modality in younger children (in those less than 5 years in the UK renal replacement registry and the European Society for Pediatric Nephrology registry and in those under 9 years in the USRDS).[7] In fact, data from the USRDS demonstrate that between 1996 and 2015, 64% of patients <20 kg received PD as their initial renal replacement therapy, in contrast to only 31.8% of those 20–50 kg. PD is particularly advantageous in the very small patient for whom maintenance of a functional and complication-free vascular access can be problematic. In school age children, home dialysis therapies, such as PD with the use of an automated PD (APD) cycling device, also facilitate regular school attendance. PD is also preferred over HD when there are contraindications to the use of anticoagulation and in children who have cardiovascular instability. Although PD should not be considered the "default option," proximity to a pediatric HD center, as well as the ability to achieve and maintain a suitable vascular access, must be considered when counseling families about different dialysis modalities available. The use of PD has increased in lower and middle income countries (LMICs) both in children and adults.[8] Importantly, the selection of a dialysis modality must be carefully discussed with the child and their family after fully informing them of the choices that are available and medically appropriate. When possible and not disadvantageous, the child and parents/caregivers' choice should be respected.

Of course, recognition of the burden of care for families that comes with the provision of this home-based dialysis therapy cannot be overestimated. In addition to the burden associated with the dialysis procedure itself, there is the burden associated with decisions regarding the type of PD solution daily, concern about complications particularly peritonitis, difficulty resolving patient drain pain, and safely managing machine errors. Families must be made fully aware of the burden of care involved with performing PD as part of the modality selection process so that appropriate support systems may be put in place. Formal assessment of the patient's and caregiver's perception of quality of life may aid in this process.[9,10] "Assisted PD," wherein a trained dialysis technician routinely visits the patients' home to set up the PD machine and/or connect and disconnect the child from PD, is available in some countries and allows more patients to receive PD by providing the required support for families.

Contraindications to the use of PD in children

Absolute contraindications.

- abdominal wall defects such as omphalocele or gastroschisis;
- bladder exstrophy;
- diaphragmatic hernia;
- obliterated peritoneal cavity; and
- peritoneal membrane failure.

Relative contraindications.

- presence of ileostomies and colostomies;
- infants with significant organomegaly;
- inadequate living situation for home dialysis;
- lack of appropriate caregiver support; and
- impending/recent major abdominal surgery.

There are no large-scale studies in pediatrics that provide evidence of a correlation between residual kidney function (RKF) and patient outcome in children receiving PD. However, in a single-center observation of a pediatric PD population, it was shown that superior growth velocity occurred in a group of children with RKF versus a group of children without RKF, despite the achievement of a similar mean total solute clearance in the two groups of patients.[11] Thus, it is possible that growth, as well as achievement of solute clearance goals, benefits from RKF.[12,13] In addition, there is some evidence that pediatric patients on PD therapy lose RKF at a slower rate than patients on HD therapy.[14,15]

Hydration status and blood pressure

Assessment of hydration status

We suggest assessing the patient's dry weight at each clinic visit with clinical evaluation, including measurement of weight and blood pressure (BP), laboratory parameters, and objective measurements of fluid status using bioimpedance spectroscopy, where available, in order to help guide the PD prescription and ultrafiltration requirements.

Level of evidence—Grade 2C

Rationale. Clinical evaluation is the most frequently used method to assess a patient's hydration status. Physical examination for edema, BP measurement, and laboratory parameters, such as hemoglobin/hematocrit and serum albumin levels, has routinely been used to assess the fluid status of patients on PD.

The presence of erythropoietin-stimulating agent (ESA)-resistant anemia can be indicative of a state of hypervolemia. In a study of anemia management in more than 1400 children by the International Pediatric Peritoneal Dialysis Network (IPPN), anemia that was poorly responsive to ESAs correlated with a greater prevalence of hypertension, left ventricular hypertrophy, and hypoalbuminemia, all likely due to hypervolemia.[16]

Additional methods to evaluate the fluid status of the PD patient include bioimpedance spectroscopy (BIS), measurement of circulating natriuretic peptide, lung ultrasound for extravascular lung water or lung B lines, inferior vena cava diameter and its collapsing index, and heavy water dilution studies. However, the data pertaining to the use of these methods in children are very limited. In a prospective, observational study in children on dialysis (PD and HD), it was suggested that BIS can serve as an objective method for the assessment of hydration status.[17] In this study, there was a poor correlation between clinical assessment of "dry weight" and BIS determined weight, with the BIS determined weight showing a strong correlation with peripheral pulse pressure, higher *N*-terminal pro-brain natriuretic peptide, and left ventricular end-diastolic diameter. The study also noted a marked discrepancy between BP and hydration status, suggesting that factors other than volume overload may contribute to high BP in some children on dialysis.[17] It should be taken into account that muscle wasting and hypoalbuminemia may also result in the overhydration of tissues.

Management of hydration status

We suggest that euvolemia and normotension be achieved in the child on PD through:

- dietary sodium and fluid restriction;
- promoting residual diuresis and use of RAS inhibitors (with appropriate monitoring for hyperkalemia and temporary discontinuation during episodes of dehydration);
- modification of the dialysis prescription; adjusting the fill volume, dwell time, and/or dialysate dextrose concentration can be assisted by assessment of the peritoneal membrane transport capacity with the Peritoneal Equilibration Test (PET). In patients suspected of having developed altered peritoneal membrane transport characteristics during the course of CPD, repeating the PET should be considered (practice points);
- use of icodextrin to enhance ultrafiltration.

Level of evidence—Grade 2D

Rationale. Most children on PD will require dietary sodium and fluid restriction to achieve/maintain euvolemia and a normal BP. Salt restriction should be instituted with caution in children with high RKF and/or dialysis-related sodium losses as salt depletion may result in hypotension and impaired growth. Rarely, it can also result in severe complications, such as anterior ischemic optic atrophy and blindness.[18] The pediatric-specific recommendations pertaining to salt and fluid management provided in the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for BP management in CKD, the Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents, and the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline for Nutrition in Children with CKD should be followed to help guide salt and water management.[19–21]

The PD prescription is designed to optimize fluid removal in most patients.[22] Components of the prescription should include the lowest possible dialysate dextrose

concentration required to achieve the desired ultrafiltration volume. Hypertonic solutions should be discouraged because of the injury to the peritoneal membrane that may occur and compromise/prevent long-term membrane function for dialysis. Alternative PD solutions, such as those using icodextrin as the osmotic agent, should be considered in situations when enhanced ultrafiltration is desired without exposing the peritoneal membrane to PD solutions with a high dextrose concentration.[23] In particular, icodextrin improves the long-dwell ultrafiltration volume in high and high-average transporters and improves phosphate clearance. Of note, icodextrin reabsorption may occur and it is not as efficacious in younger children[24] as it is in older children and adults. The efficacy may, in part, be influenced by the dialysate fill volume used.[23] In children who are hypertensive or in whom there is evidence of volume overload, ultrafiltration generally should be targeted to be positive for all daytime or nighttime exchanges. In particular, the drain volume should be positive after the overnight dwell of continuous ambulatory PD and the daytime dwell(s) of CCPD to maximize solute clearance and ultrafiltration volume.

The impact of the APD prescription on daily ultrafiltration volume was assessed in the IPPN cohort. From a total of over 7800 observations in nearly 2500 children, a mean daily UF volume of 600 $\pm$ 680 ml/m^2 was achieved. After adjusting for age, time on PD, and RKF, ultrafiltration volume was directly and significantly influenced by the average dextrose concentration (240 ml more UF per percentage increase in glucose concentration), number of cycles, and both the daytime and nighttime fill volumes and was inversely associated with the dwell time (34 ml less UF per hour increase; $p < 0.001$).[25]

As suggested above, the dialysis dwell time should be adjusted to optimize ultrafiltration, guided by the results of the PET. A reassessment of the PET may be especially useful in patients suspected of having altered peritoneal membrane transport characteristics (e.g. history of peritonitis and long-term use of hypertonic PD solutions). Whenever possible, the fill volumes should also be optimized, targeting a fill volume of 600–800 ml/m^2 body surface area (BSA) in children under 2 years and 1100–1400 ml/m^2 BSA in older children.[26] A stepwise increase in volume as tolerated by the patient is recommended. In some cases, measurement of the intraperitoneal pressure (IPP) can be considered to assist in the fill volume prescription so as not to exceed a safe IPP. An upper limit of approximately 14 cm of H_2O, which corresponds to a mean fill volume of 1400 ml/m^2, is considered a safe IPP limit for most children.[26] Severe constipation may lead to an increase in IPP, and the appropriate use of laxatives can help prevent this common complication. Care to avoid clinical overfill and a high IPP is essential as it may result in emesis, poor ultrafiltration as a result of enhanced lymphatic uptake, and the development of hernias.

It may be possible to modify the PD prescription to promote small pore transport and achieve improved sodium and fluid management by using an adapted automated PD program. In adapted automated PD, sequential short- and longer-dwell exchanges, with small and large dwell volumes, respectively, are used.[27] A crossover trial in adults and a pilot study in children suggest that sodium and fluid removal are increased by adapted automated PD, leading to improved BP control when compared with conventional PD but require further prospective crossover studies in adults and children for validation.

In patients with RKF, exposure to aminoglycosides and other nephrotoxic agents should be avoided. Prompt resolution of insults (such as infection and dehydration) that could result in acute kidney injury (AKI) and impaired diuresis is imperative to control the hydration status. Diuretic use should also be considered as a means to maximize urinary salt and water excretion. The use of diuretics may be preferred over increasing the dialysate dextrose concentration to achieve euvolemia in patients with RKF, as peritoneal membrane injury may occur with hypertonic solutions. The use of diuretics may also be particularly beneficial in LMICs, where icodextrin-based solutions may not be available. In an analysis of 401 incident pediatric PD patients with RKF followed prospectively in the IPPN registry, those who received diuretics were 80% less likely to develop oligoanuria (<100 ml/m^2/day) compared to those who did not receive diuretic therapy.[28]

The use of RAAS inhibitors, such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB), should be considered in the PD patient who requires antihypertensive medications and has RKF. The use of an ACE inhibitor in children with CKD has been associated with marked slowing of kidney deterioration.[29] However, the IPPN also found that the use of RAAS inhibitors significantly increased the risk of hyperkalemia ($p = 0.04$).[25] Close monitoring for the presence of hyperkalemia is, in turn, mandatory when an ACE inhibitor or ARB is used for patients receiving PD. Parents must be educated about temporarily discontinuing RAAS inhibitors when the child is at risk for dehydration, such as during an intercurrent diarrheal illness.

Solute clearance on PD

We suggest that the PD prescription should be adjusted with the goal of achieving a normal serum phosphate level. A total minimum weekly Kt/V_{urea} of 1.7 should be targeted in children on PD, with modifications based on regular assessment of clinical well-being and laboratory parameters, if required.

Level of evidence—Grade 2D

Rationale. Enhancement of phosphate removal and achievement of a normal/near normal serum phosphorus level in

children on PD is an important clinical target because of the associated decreased potential for cardiovascular disease and poorly controlled CKD-mineral bone disorder (MBD). The efficiency of phosphate removal is related to contact time between dialysate and the peritoneal membrane. As a result, extended dwell time will typically enhance phosphate removal. In patients with an elevated phosphate level and receiving APD, the long day dwell should be optimized. In a study of 35 children on APD, the 24-h dialytic phosphate clearance was assessed together with peritoneal equilibration tests. The dialytic phosphate clearance strongly correlated with the total dialysate turnover and the prescribed number of cycles and was better predicted by the 2-h dialysate/plasma phosphate ratio than by creatinine equilibration characteristics on the PET test.[30] In the IPPN registry data, the mean serum phosphate level was 1.8 $\pm$ 0.5 mmol/l and directly correlated with the ultrafiltration volume but inversely correlated with the number of cycles, dwell time, and icodextrin use.[25] On multivariate analysis, serum phosphate decreased by 0.17 mg/dl per hour dwell time and by 0.03 mg/dl per added cycle.[25] Importantly, normal phosphate levels cannot be achieved without dietary restriction and phosphate binders in most dialysis patients, and their relative contributions, as well as the contribution of RKF on the serum phosphate level frequently play a role in determining the dialysis requirement.

As for urea clearance, there are no definitive data in children that demonstrate a correlation between either dialytic or total (RKF and dialysis) Kt/V_{urea} and patient outcome or survival. Of interest, however, studies on HD in children that have shown that increased growth rates are associated with a higher Kt/V delivered through intensified dialysis regimens compared to conventional three times per week HD.[31] The IPPN registry has demonstrated a mean dialytic Kt/V_{urea} of 2.24 $\pm$ 0.84 in its CPD patient cohort. The APD prescription influenced Kt/V_{urea} with daily ultrafiltration volume, number of cycles, and both daytime and nighttime fill volumes having a significant direct impact on Kt/V_{urea} ($p < 0.001$ for all). The strongest effect was seen for ultrafiltration volume; Kt/V_{urea} increased by 0.02 per 100 ml increase in ultrafiltration/day (adjusted for body surface area).[25] Empirically, based on weak evidence from the adult experience pertaining to a contribution of achieved urea removal to patient outcome, we suggest that a total (dialysis and RKF) weekly Kt/V_{urea} of 1.7 be targeted in children. However, children with Kt/V_{urea} <1.7 who are otherwise doing well on PD based on a close and repeated assessment of clinical and laboratory parameters should not have their PD prescription increased for the sole purpose of meeting this target.

Constipation is a very common problem in patients on PD that can impact on PD drainage as well as cause catheter migration. Families must be made aware of the need to monitor bowel movements and use laxatives, usually prophylactically, to avoid constipation.

Individualized PD prescription—Practice points

While the goal of PD therapy is to optimize fluid management and solute clearance, this must be considered in the context of the child and family's expectations of dialysis and quality of life, encouraging the child to enjoy their school and free time with family and friends as much as possible.[32] Flexibility in the dialysis program, such as the allowance for an occasional dialysis-free night, may be considered in children with substantial RKF. Similarly, excessive fluid removal, especially with strong dextrose-based dialysate, should be minimized in the child on APD to limit the likelihood of the child feeling thirsty and nauseous the following morning, thus affecting their school attendance or performance. The use of remote monitoring systems may allow for appropriate monitoring of the child's well-being and adjustment of the PD prescription without frequent hospital visits. Negotiating a suitable dialysis program with the patient and family ("shared decision-making"), and aligning the goals of what both the physician and patient consider to be "optimal" dialysis, may go a long way in achieving a successful long-term outcome.

In all cases, the PD prescription should be designed to meet the medical and psychosocial needs of the individual patient and family as a component of high-quality care. Whereas ultrafiltration, water and sodium balance, and solute purification are dialysis treatment targets which necessitate appropriate modification of the fill volume, dwell time, and PD solution, equal attention must be given to outcome parameters, such as growth, nutritional status, school attendance, and quality of life when assessing the efficacy of the dialysis regimen and the overall treatment regimen. Growth should be closely monitored with attention to nutritional intake, management of CKD-MBD, control of acid–base status, sodium supplementation as needed, and, potentially, recombinant growth hormone therapy. The provision of a dialysis regimen using nocturnal APD facilitates school attendance for the age-appropriate PD population. Standardized assessments of health-related quality of life (HRQoL) should be conducted to identify areas in which alterations in the overall treatment regimen or additional support may be required.[9,33] In particular, the "burden of care" associated with the provision of home PD by the parents/caregivers should be closely monitored with support services made available as needed through the dialysis team.[10]

Additional practice points

Quality improvement program such as the Standardizing Care to Improve Outcomes in Pediatric ESRD initiative has successfully demonstrated a decrease in peritonitis rates through rigorous compliance with PD catheter care bundles.[34] Improvement science methods such as this have

helped identifying the primary drivers directly linked to the outcome of peritonitis, as well as the role that factors such as health literacy and patient and family engagement strategies can have in improving the outcomes for children on PD.[35]

The nondialysis management of all infants, children, and adolescents who receive chronic PD should be conducted in accordance with the pediatric-specific content of the following guidelines: the KDIGO Guidelines for the Management of Anemia in CKD,[36] the KDIGO Clinical Practice Guidelines for the Management of Blood Pressure in CKD,[20] the Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents,[21] the KDIGO Guidelines for Lipid Management in CKD,[37] the KDOQI Clinical Practice Guidelines for Nutrition in Children with CKD,[19] and the guidelines for CKD-MBD management from the European Society of Pediatric Nephrology.[38,39]

Clinical management of the pediatric patient who receives chronic PD mandates attention to a wide range of clinical issues that may be present as a result of the multiple organ systems that are affected by ESKD. Incorporation of the numerous published recommendations into clinical care is intended to help optimize care. It is recognized that the majority of recommendations are based on a combination of evidence and expert opinion.

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