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Role of Ultrafiltration in Peritoneal Dialysis: A Review

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With the widespread availability of dialysis, the lives of hundreds of thousands of patients with ESRD have been prolong. Peritoneal Dialysis (PD) is an established modality of renal replacement therapy for patients with end stage renal disease (ESRD) worldwide. The success of PD depends on the efficient removal of both solute and fluid. It has been observed that ultra filtration failure (UFF) in PD patients particularly with high transport characteristics results in fluid overload and increased cardiovascular mortality despite adequate solute clearance. The amount of excess fluid removed as a result of osmotic gradient created by glucose / icodextrin present in the PD fluid during the PD exchange is called Ultra filtration (UF).

The amount of UF has been correlated with patient survival in PD patients. UF was predictive of survival in anuric automated peritoneal dialysis (APD) patients in the prospective observational European Automated Peritoneal Dialysis Outcome Study (EAPOS).[1] The baseline ultra filtration below 750 mL/day was associated with poorer survival, but the time-averaged ultra filtration was not when analyzed time dependently. In contrast, ultra filtration analyzed as a continuous variable was a significant factor for survival in the time-dependent analysis of anuric patients in Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD).[2] The European best practice guideline working Group on PD set an arbitrary target that the minimum net UF in anuric peritoneal dialysis (PD) patients should be 1 L/day.[3] However, the International Society for Peritoneal Dialysis believes that no numerical target for UF can be formulated using the present data and target should be individualized.[4]

Ultra filtration failure (UFF)/membrane failure has now become one of the important reasons for technique failure in PD. In view of disproportionately greater effect on fluid removal than solute removal in cases of peritoneal membrane function alterations, most cases of membrane failure are due to failure to achieve adequate UF. Net UF has been shown to decrease by as much as 30%-40% from baseline in most patients on PD for more than 3-4 years, with peritoneal clearance of small solutes increasing or being stable.[5] Prakash et al[6] from India has reported UFF as the most common (15.5%) non-infectious complication of CAPD in their study.

Prevalence and Definition of UFF

UFF usually occurs in patients on long term PD, although it can occur at any stage of PD. Initial studies were based on clinical signs of UFF and

not on standardized tests. In 1990 Heimburger et al.[7] from Sweden have demonstrated the cumulative risk for permanent loss of net UF capacity to be 2.6% at 1 year, 9.5% at 3 years, and more than 30% for those patients on CAPD for 6 years or more. *In 2000, the International Society for Peritoneal Dialysis (ISPD) committee[8] on UFF advised performing a standardized test with 3.86%/4.25% glucose, and considered a net UF of < 400 mL after a 4-hour dwell as UFF*. Based on this criterion, studies[9,10] have demonstrated a prevalence of UFF in range of 23-36%. Accurate measurement of UF is important to detect patients with UFF. The introduction of "flush-before-fill" PD technique has led to improved peritonitis rates. However, to compensate for dialysate lost during flush-before-fill, extra dialysate was added to each PD bag and now a 2-L PD bag contains a mean volume of 2.225 L. Awareness that calculation of UF must exclude overfill volumes is necessary as it can lead to underestimation of prevalence of UFF.[11]

Approach to a patient on PD with UFF

Inability to maintain an edema-free state or their target weight despite frequent use of hypertonic exchanges and dietary restriction, increasing requirements of antihypertensive medications and recurrent admissions for fluid overload state marks for the suspicion of UFF.

A good history and a thorough physical examination are important when a patient presents with signs or symptoms of fluid overload. History related to compliance with diet and dialysis, and any significant reduction in urine output may guide us towards the reason for fluid overload state. Information pertaining to the duration over which there was occurrence of fluid accumulation is beneficial. Symptoms of UFF develop *gradually* in patients with membrane failure and increased lymphatic absorption whereas *acutely* in patients with mechanical problems (malpositioned catheter or dialysate leak).

The UFF is not always a responsible factor for the development of fluid overload in PD patients. The fluid overload state can occur with and without UFF. Broadly fluid overload can be divided in to two categories.

1. Fluid overload without UFF: The unexplained fluid overload without UFF could be because of noncompliance with diet or, dialysis prescription, and unrecognized and uncompensated loss of residual renal function (RRF), particularly in high-transporters.

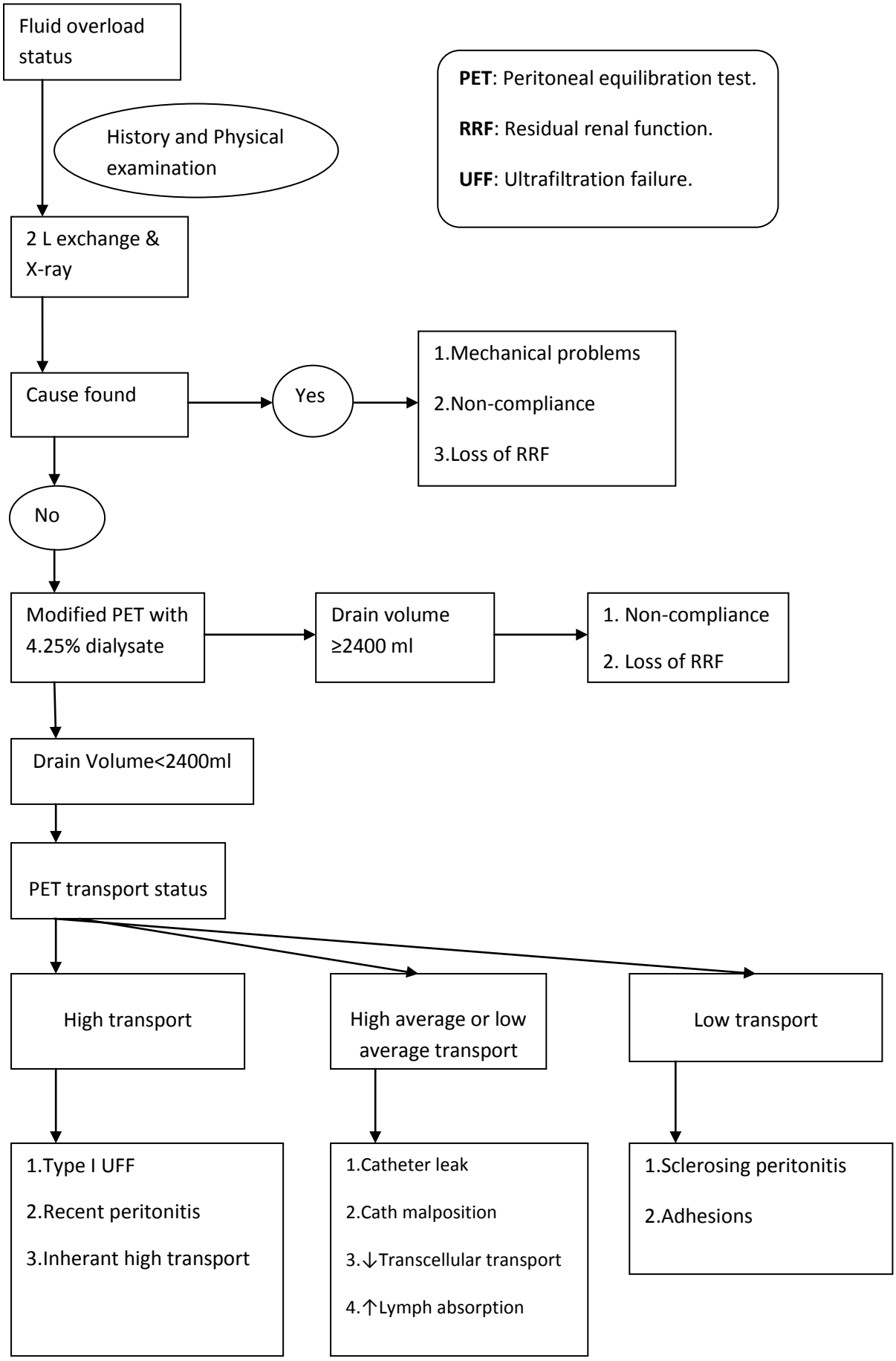
2. Fluid overload with UFF: An imbalance between the transcapillary ultrafiltration and lymphatic absorption rates results in UFF, which clinically reflects as the need for more hypertonic exchanges to control volume overload. After ruling out the mechanical causes clinically, a modified PET should be done for an algorithmic approach to differential diagnosis and management of UFF (Figure-1).

Classifications of UFF: Pathophysiologically, the following four types of UFF have been described. (Table-1)

Table-1 Types of ultrafiltration failure.

Type of Ultrafiltration Failure	Characteristics	Remarks
Type I	Large effective peritoneal surface area	High solute transport state with hyperpermeable peritoneal membrane.
Type II	Low osmotic conductance to glucose	Aquaporin dysfunction
Type III	Low effective peritoneal surface area	Abdominal adhesions Encapsulating peritoneal sclerosis
Type IV	High effective lymphatic absorption rate.	Dialysate leak to be ruled out as it is secondary cause of increased lymphatic absorption.

Figure-1: Approach to fluid overload status in a patient on Peritoneal dialysis.



Type 1 UFF: Patients of UFF with High Solute Transport (D/P Creatinine > 0.81)

This type of UFF represents the largest group of patients with inadequate UF due to peritoneal membrane characteristics. This type of UFF can also be observed in patients with inherent high transport characteristics of peritoneal membrane and during the episodes of peritonitis in PD patients.

The associated functional abnormality in this type of UFF is occurrence of large effective peritoneal surface area and subsequent membrane hyperpermeability. Type I UFF occurs probably as a result of both fibrosis and angiogenesis, resulting in a large effective surface area. Angiogenesis leads to an increased number of perfused capillaries under the fibrotic matrix, which rapidly dissipate the glucose-driven osmotic pressure, hampering the ultrafiltration. This hyperpermeability has been demonstrated as a predictor of increase in the mortality and technique failure in long term PD patients. Our study has also shown that patients' survival is inferior in high / high average transport status group as compared to the patients with Low / Low average transport status group.[12]

Etio- pathogenesis of Type I UFF

Recently, extensive research has been done to elucidate the mechanisms that are involved in the pathogenesis of peritoneal membrane failure during long-term PD.

Major factors contributing to morphologic and functional alterations of the peritoneal membrane have been

a) Uremia,
b) Peritonitis, and
c) Non-physiological PD fluids.

Uremia: Circulating factors like nitric oxide (NO), advanced glycation end products (AGEs), vascular endothelial growth factor (VEGF), and inflammatory cytokines [interleukin (IL-1β), tumor necrosis factor alpha (TNF-α), and IL-6] are all significantly increased in the uremic milieu.[13] The increase in effective peritoneal surface area is strongly related to VEGF and NO. Permeability of the peritoneal membrane and the degree of angiogenesis correlates directly with the expression of VEGF in the peritoneum. Uremia per se leads to thickening of the sub-mesothelial zone and mild vasculopathy, as confirmed from the peritoneal biopsy registry data.[14]

Non-physiologic nature of PD fluids: The acidic nature and the inevitable formation of glucose degradation products (GDPs) make the commonly used dextrose based PD fluids non-physiologic. Glucose is a pro-inflammatory agent and has an additional profibrotic effect leading fibrosis and angiogenesis by activation of various pathways. The factors responsible for inducing peritoneal fibrosis and angiogenesis are enumerated in Table 2. This angiogenesis resembles neo-vasculari-zation seen in proliferative diabetic retinopathy and makes the peritoneal membrane highly permeable.

Table-2 Inducers of Peritoneal Fibrosis and angiogenesis

Inducers of Peritoneal fibrosis	**Inducers of Angiogenesis**
Stimulation of transforming growth factor (TGF)-1β Activation of protein kinase C. Reactive oxygen species (ROS) - Oxidative stress Local Angiotensin II production Advanced glycation end products (AGEs) Plasminogen activator inhibitor (PAI)-1	Glucose degradation products (GDPs) Advanced glycation end products (AGEs) Vascular endothelial growth factor (VEGF)

Mesothelial cells undergo epithelial-mesenchymal transition (EMT): Mesothelial cells (MC) play an active role in peritoneal membrane alteration. Peritoneal MCs show a progressive loss of epithelial phenotype and acquire myofibroblast-like characteristics by an epithelial-mesenchymal transition (EMT) upon initiation of PD.[15] The resultant effect of this EMT is not only peritoneal fibrosis, but also angiogenesis mediated through upregulation of VEGF pathway and ultimately leading to peritoneal membrane failure.[16]

Recent Peritonitis: During an episode of acute PD peritonitis, UF is impaired transiently and

fluid overload status is commonly seen. The high solute transport status due to peritonitis leads to rapid loss of osmotic gradient. The infection-induced hyperpermeability is probably due to proinflammatory cytokines, prostaglandins and increased NO synthase activity. A change in the PD prescription for adequate ultrafiltration is needed with inclusion of either higher concentration dextrose solution or more number of rapid exchanges or icodextrin. There are several studies which support use of icodextrin during peritonitis[17]. Although clinical recovery of peritonitis occurs in few days, remesothelia-lization does not occur immediately and may be delayed by up to 6 weeks. Hence PET should be delayed by atleast 4-6 weeks after an episode of peritonitis.

Type – II UFF – Aquaporin dysfunction; patients with low average –high average solute transport D/P Creatinine of 0.5-0.8.

There is a subset of patients with UFF in whom no associated increases in solute transport (for creatinine or glucose), residual volume, or lymphatic absorption (LA) rate could be demonstrated.[18] However, in all these patients, normal sodium sieving effect (drop in dialysate sodium concentration) was lost. This selective defect in water transport has been attributed to AQP-1 channel (ultrasmall pore) dysfunction, rather than deficiency in peritoneal membrane.

Type III UFF - Patients with Low-Solute Transport (D/P Creatinine < 0.5)

A much less common cause for UFF is that associated with low-solute transport (D/P creatinine < 0.5) (Figure-1), which often results from conditions leading to a severe reduction in effective peritoneal membrane surface area and permeability[19]. Therefore, signs and symptoms of both fluid overload and inadequate solute removal can be present. This is observed in patients who have recurrent and relapsing peritonitis, sclerosis of the peritoneal membrane (sclerosing peritonitis), and extensive intra-abdominal adhesions.

Encapsulating Peritoneal Sclerosis (EPS): EPS is a rare complication of long term PD, nearly only occurring in patients longer than 3-5 years. Most of the initial reports of EPS were from Japan and Australia[20,21]; more recently, there has been an increasing number of reports of EPS from different parts of the world[22]. Incidence of EPS ranges from 6.4% at 5 years to 19.4 % at 8 years in Australian registry data.[23,28] An *ad hoc* committee of the ISPD defines EPS as: "A clinical syndrome with persistent, intermittent or recurrent presence of intestinal obstruction with or without the existence of inflammation parameters and the existence of peritoneal thickening, sclerosis, calcifications and encapsulation confirmed by macroscopic inspection or radiological findings"[24]. It is associated with high morbidity related to bowel obstruction and malnutrition and high reported mortality of around 50%, usually within 12 months of the diagnosis[20,25]. The amount of glucose exposure and the occurrence of (severe) peritonitis episodes have been implicated for the onset of EPS. Contrary to the reports of post-transplant EPS from UK and Dutch units[22,26], there are also isolated reports of dramatic resolution of established EPS[27] following renal transplantation. *The reader is advised to refer the ISPD statement on EPS for a detailed discussion*[28].

Abdominal Adhesions

Extensive intraabdominal adhesions can occur in patients after recurrent or severe peritonitis, catastrophic intraabdominal events, or complicated abdominal surgery[29]. There is a decrease in the effective surface area of the peritoneum as adhesions limit dialysate flow throughout the abdominal cavity. This compromises both solute transport and UF. Radiological diagnosis can be made by intraperitoneal infusion of a radiographic contrast material through the dialysis catheter with plain x-ray or CT visualization, or with the intra-peritoneal infusion of a radioisotope and peritoneal scintigraphy[30,31]. Unequal distribution of peritoneal fluid will be seen if adhesions are

present despite changes in patient position or posture.

Type IV UFF: Increased Lymphatic Flow

Net ultrafiltration and solute clearance are inversely related to lymphatic absorption of peritoneal fluid. As there are no alterations in dialysate fluid solute concentrations in these patients, the D/P creatinine ratio does not change with increased lymphatic flow, although net UF can be significantly decreased.

As measured with intraperitoneal dextran-70 the mean value of the lymphatic absorption rate in PD patients during their first 2 years of PD treatment, averages 1.52 mL/min, when a 2-L exchange is used[32].

Factors influencing lymphatic absorption are dialysate volume, intraperitoneal pressure, and probably mass transfer area co-efficient of peritoneal membrane.

Factors not influencing lymphatic absorption are body surface area, tonicity of the dialysate fluid, position of the patient and also probably duration of PD.

Mechanical problems which can present with fluid overload status:

Mechanical problems like peritoneal leak and malposition of catheter can present with a low drain volume coupled with either high-average or low-average transport (D/P creatinine 0.5 to 0.81). It mimics like UFF, however is not UFF in true sense.

Dialysate Leak: Dialysate leaks from the intraabdominal cavity to extra-abdominal tissues, usually the abdominal wall, result in a decrease in UF drain volume. Although the reason of low drain volume is obvious, and the fluid leaked into the interstitium is subsequently removed by the lymphatic system and therefore technically falls into the category of UFF secondary to increased lymphatic flow.

An extra peritoneal dialysate leak is frequently accompanied by

a) Abdominal wall hernia,
b) History of multiple abdominal surgeries, or
c) Patent processus vaginalis

Edema localized to the abdominal wall, upper thigh or genitalia is usually evident. Most reports indicate that the incidence of dialysis leakage is somewhat more than 5% in PD patients[33,34]; Patients with ESRD due to enlarged cystic kidney diseases are more prone to the development of abdominal wall defects[33].

Diagnosis of dialysate leak: Leak may be confirmed by utilizing an appropriate radiographic technique. These include:

a) Intraperitoneal infusion of radiographic contrast through the catheter followed by plain X-ray or Computed tomography scan [30] **or**
b) Intraperitoneal infusion of a radioisotope evaluated with peritoneal scintigraphy[35]**or**
c) MRI without contrast (the dialysate itself functions as contrast material).

Peritoneal membrane function is not compromised in patients with dialysate leaks. Therefore, peritoneal transport as evaluated by the PET is not changed compared with a patient's baseline study.

Catheter Malposition: Mechanical problems, such as a malpositioned catheter, resulted in UFF in 7% of patients in one center[36]. In a retrospective analysis of a cohort of 567 consecutive ESRD patients initiated on CAPD from January 2002 to July 2005 at our centre, 172 had mechanical and catheter related problems. Catheter malposition was seen in 41 % of these patients at some point of time. Catheter removal or repositioning was required in 24% of them. (Unpublished data)

Catheter malposition may occur because of:

a) (common) Migration of catheters originally in good position due to entanglement by omentum,
b) Improper initial catheter placement, or
c) Adhesions from previous surgery[37].

A malpositioned catheter does not drain the peritoneal cavity effectively and leads to an increase in residual volume leading to dilution of the glucose concentration in the freshly instilled dialysate. This decreases the osmotic gradient and

thereby decreases the UF rate without much effect on solute transport. The diagnosis of a malpositioned catheter is easily made with an X-ray.

Clinical clues for mechanical problems

Dialysate flow "positional" / incomplete	Localized edema (abdomen or inguinal region)
↓	↓
Suspect malpositioned catheter	Suspect peritoneal leak
↓	↓
A flat-plate radiograph of the abdomen	CT or MR Abdomen

Prevention and Treatment of UFF

General Guidelines

Regular monitoring: Emphasis should be given for regular monitoring of PD management protocols involving weight (desired/target), course of RRF and UF achieved with the current dialysis prescription. Special emphasis is to be made for routine performance of PET at regular intervals. The volume status of patients on PD should be used as an important indicator of dialysis adequacy. Particular emphasis should be placed on the blood pressure control with fluid removal alone.

Dialysis/diet compliance: Noncompliance with the dialysis prescription, as estimated can range from 13% to 78% of patients[38,39]. Noncompliance with dialysis can be documented objectively by comparing measured to calculated creatinine production, but these are variable and inaccurate[39]. An estimate of dialysate use can be obtained through the screening of receipts or discussing with the pharmacist who issues dialysis bags to the patient. Most common reason for dialysis non compliance in our country is the financial burden with PD. Education and positive reinforcement may help improve this problem in a motivated patient. Detailed counseling and regular re-enforcement of guidelines can decrease the occurrence of dietary noncompliance.

Protection of RRF: At the initiation of PD, most patients still have RRF contributing to better middle and larger molecular weight toxin clearance and better volume homeostasis control. RRF continues to decline on dialysis, which is associated with a significant decrease in urine volume and derangement of volume homeostasis.

The following measures could be taken to preserve RRF:

a) Avoidance of nephrotoxic agents including intravenous contrast, antibiotics (e.g., aminoglyc-osides) and Non steroidal anti-inflammatory drugs (NSAIDS).
b) Prevention of hypotensive episodes
c) Use of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARBs) reduces the rate of decline in RRF and possibly delays the development of complete anuria in patients performing PD[40,41].
d) ISPD recommends that 24-hour urine volume and clearances should be measured regularly and at an appropriate frequency (every 1 to 2 months if practicable, otherwise no less frequently than every 4 to 6 months) so that the PD prescription can be adjusted accordingly[42].

Diuretic use: Urine volume can be successfully increased in patients with RRF by using large doses of loop diuretics with or without metolazone. Although these agents do not help preserve RRF, they do increase urine output[43]. Significant ototoxicity[44] is an important adverse effect which can be reduced with avoidance of IV boluses or high dose infusions and avoidance of other ototoxic medications like aminoglycosides.

Appropriate dialysis prescription: Choosing the right prescription for the peritoneal transport type of the patient is important. Patients with high and high-average transport can achieve adequate UF using APD (four to five night cycles and long day dwell with icodextrin) and lower total glucose exposure than with PD[45].

Control of hyperglycemia: Hyperglycemia can adversely affect the maintenance of an osmotic gradient across the peritoneal membrane in diabetics and its control can improve UF without the need to use hypertonic glucose solutions unnecessarily.

Preservation of Peritoneal Membrane Function and Prevention of UFF: The most important therapeutic option is the prevention of UFF.

a. Reduction of the occurrence of peritonitis → can be achieved with[46]

i. Appropriate patient training and retraining in aseptic techniques,
ii. Universal adoption of exit site antibiotic prophylaxis (either gentamicin or mupirocin creams) and
iii. Use of the widely applied double-bag system, which prevents extra disconnections.

b. Reduction of peritoneal glucose exposure and the development of more biocompatible dialysis solutions.

i. Preservation of the residual renal function.
ii. Diuretic usage can lead to more fluid removal by the kidneys, instead of increasing the osmolality of the dialysate.
iii. Alternative solutions that can replace glucose for one exchange/day – Icodextrin and amino-acids.
iv. Temporary cessation of PD has been used in a few patients with high small solute transport characteristics with some success.

Therapeutic Guidelines for Specific Diagnostic Categories

Table-3: Treatment options in a patient with ultrafiltration failure.

Cause of UFF	Treatment Option
High transport status	Avoid long dwells Use icodextrin
Loss of functional peritoneum	Transfer to HD when RRF is absent Adhesionolysis if indicated
Aquaporin dysfunction	Avoid hypertonic glucose Use icodextrin Temporarily discontinue PD?
Increased lymphatic absorption	Avoid large volumes of dialysate Avoid long dwells

High transport Status: Treatment interventions in patients with high small solute transport need to address the rapid dissipation of the osmotic gradient. (Table-3) The most appropriate intervention is the use of a glucose polymer such as icodextrin[47-50]. Dialysis solutions containing icodextrin have been shown to be superior to glucose-based solutions in achieving net ultrafiltration during long dwells in majority of patients and particularly in high transporters. In a study comprising 48 patients from our centre who were started on icodextrin night dwell, significant increase in mean ultrafiltration was seen after shifting the patients to icodextrin (875±450 Vs 1350±525 ml, P=0.001)[unpublished data]. Forty-five percent of these patients were started on icodextrin for reasons of UFF.

In a recent study by Dousdampanis et al[51], two exchanges of icodextrin of eight hours each per day has been tested in patients with UFF with good results in ultrafiltration over a period of six months with no obvious adverse effects related to theoretical increase in maltose levels.

Although icodextrin- based UF may improve volume balance in PD patients[52], there is still a high incidence of fluid overload syndrome, hypertension, and congestive cardiac failure in this population. Freida et al[53] from Sweden have studied a novel combination dialysate fluid, a mixture of colloid(icodextrin) and crystalloid(dextrose) in a small cohort of patients with impressive results in both fluid and sodium removal which was not achieved by dextrose 3.86% or icodextrin alone.

In areas where icodextrin is not available, shortening dwell time is the preferred approach. In CAPD patients this can be achieved with use of an automated night-time exchange device. This approach will shorten dwell time and has the additional benefit of improving small solute clearance with little impact on patient lifestyle.

Loss of Functional Peritoneum: If therapeutic targets for either azotemia and volume homeostasis cannot be met with PD, then adjunctive hemodialysis or permanent transfer to hemodialysis may be required. In patients with RRF, use of loop diuretics may allow achievement of adequate fluid balance while continuing on PD.

Aquaporin Dysfunction: Patients with aquaporin dysfunction continue to have significant UF via non-aquaporin pathways. This can be enhanced by the use of icodextrin in long dwells allowing for sustained fluid removal[49,50]. For the glucose-based exchanges, increasing the dextrose concentration will not be beneficial.

In patients with **increased lymphatic absorption** the following intervention may benefit**:**

a. Short dwell times with high tonicity of dialysate fluids
b. Avoid large dwell volumes
c. ? Oral bethanechol chloride[54] – cholinergic agent (hypothesis: An increase in cholinergic tone appears to contract the subdiaphragmatic lymphatic stomata, thereby reducing lymph flow.)

Treatment of dialysate leaks and catheter malposition: Treatment of peritoneal leaks is aimed at repairing the defect in the peritoneum. Leaks associated with hernias usually require surgical repair of the hernia. Temporary transfer to HD for several weeks until adequate healing has occurred has been standard in the past but a recent report from Shah et al[55] illustrates that this is not compulsory. Leaks that occur in the absence of a hernia usually represent a tear in the parietal peritoneum. These patients frequently have a history of multiple abdominal surgeries, pregnancies, recent corticosteroid usage, or abdominal straining (coughing, Valsalva maneuver).

Repositioning of the catheter tip can be done for catheter malposition with either open or laparoscopic methods. However, recurrence is common and may require replacing through a new exit site. Nonsurgical manipulation of catheter position using a stiff guide wire under fluoroscopic guidance has also been reported[56]. A swan neck catheter is now recommended for recurrent malpositioning[57].

Treatment of EPS: Treatment of a patient diagnosed to have EPS is one of a multidisciplinary approach.[28]

a) **Stopping PD** and switch over to HD.
b) Nutritional supplementation.
c) **Drug therapy**: Corticosteroids, Tamoxifen, Immunosuppression – doubtful benefit.
d) **Surgery** - has an important and definitive role in the treatment of EPS and that, in experienced hands, surgery results in high rates of improvement in symptoms and survival[28].

Conclusion

The risk of ultrafiltration failure increases with the duration of PD. Assessment of PET and RRF should be done at regular intervals as per ISPD guidelines. Modified PET is an important tool in the evaluation of patients presenting with fluid overload status where the etiology is not overtly obvious.

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