

## Medical Policy



### Title: Ultrafiltration in Decompensated Heart Failure

#### Professional

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### DESCRIPTION

Ultrafiltration is a technique being evaluated for removal of excess fluid from patients with volume overload and heart failure. Ultrafiltration removes fluid from the blood by using pressure differentials with dialysis equipment or similar filtration devices.

### Background

Heart failure is a relatively common problem and frequently results in hospitalizations and readmissions. Various approaches are being explored in treating this condition, especially when it is refractory (unresponsive) to conventional therapy. Ultrafiltration is one technique receiving increasing notice for a possible role in hospitalized patients with marked volume overload from heart failure. Ultrafiltration is a process utilized to remove fluid from the blood by using pressure differentials during treatment with a dialysis machine or similar filtration device.

Proponents of this technique suggest that it may offer the potential for greater and more expeditious volume and sodium removal compared with conventional therapies. Ultrafiltration is generally used for those with decompensated heart failure whose fluid overload is unresponsive to medical management. In recent studies, this technique is also referred to as aquapheresis. Work is also beginning on newer devices that allow continuous ultrafiltration in ambulatory patients.

### **Regulatory Status**

In June 2002, the Aquadex™ FlexFlow™ System (CHF Solutions, Brooklyn Park, MN) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. An updated/amended 510(k) approval (classified as a high permeability dialysis system) was given in September 2007 following modifications. The FDA determined that this device was substantially equivalent to existing devices for use in temporary (up to 8 hours) ultrafiltration treatment of patients with fluid overload who have failed diuretic therapy, and for extended (longer than 8 hours) ultrafiltration treatment of patients with fluid overload who have failed diuretic therapy and require hospitalization.

### **POLICY**

The use of ultrafiltration is considered **experimental / investigational** in patients with compensated heart failure who are being treated in the outpatient setting.

### **RATIONALE**

The most recent literature review covers the period of April 2013 through May 23, 2014.

In evaluating this technology, randomized controlled trials (RCTs) are needed to determine the comparative efficacy of ultrafiltration with conventional therapy. Heart failure is a condition with a variable natural history and multiple confounders of outcome; therefore, other study designs do not provide adequate evidence to control for these factors. The primary question that clinical trials should address is whether ultrafiltration improves important health outcomes. While removal of fluid and sodium (and weight) is important, these are viewed as surrogate outcomes. Information will be needed about impact on survival, hospitalization, complications, and quality of life for this treatment compared with comparable groups receiving conventional treatment. Because this treatment does not directly affect cardiac function, the overall impact on outcomes is difficult to predict. The studies published to date are very limited, both in terms of study population and in duration of follow-up.

### **Literature Review**

The evidence on the efficacy of ultrafiltration consists of 1 multicenter RCT, the UNLOAD trial, and several smaller, single-center RCTs. The UNLOAD trial reports on physiologic and clinical outcomes, while the single-center studies primarily report on physiologic outcome measures.

### Systematic Reviews and Meta-Analyses

Four systematic reviews (including 2 meta-analyses) of RCTs have been published. (1-4) All of the reviews found ultrafiltration resulted in significantly greater weight loss and fluid removal than diuretic therapy. (1-4) Three reviews found no significant differences in adverse events, (1,2,4) and 1 found the evidence to be inconclusive. (3) Two reviews reported on all-cause mortality and rehospitalizations and found no significant differences between ultrafiltration and diuresis. (1,3) Additionally, 1 review found no significant differences in dyspnea score or increase in creatinine levels. (1) Limitations reported in the review included small studies sizes and publication biases.

### Randomized Controlled Trials

UNLOAD trial. The UNLOAD trial was a nonblinded trial that involved 200 patients hospitalized for heart failure and hypervolemia randomly assigned during the first 24 hours of hospitalization to ultrafiltration or usual care (diuretics). (5) The study was conducted during 1 year at 28 U.S. centers. Primary efficacy end points were 48-hour weight loss and dyspnea score (1-7 Likert scale). Primary safety end points were changes in blood urea nitrogen, creatinine, and electrolyte levels throughout hospitalization and 90-day follow-up, and episodes of hypotension requiring therapeutic intervention at 48 hours. At least 13 secondary efficacy end points are also listed, including length of index hospitalization, quality-of-life assessments throughout follow-up, and resource utilization (rehospitalization for heart failure, unscheduled office and emergency department visits) during follow-up. Results showed a weight loss of 5.0 versus 3.1 kg from baseline at 48 hours ( $p=0.001$ ) for the ultrafiltration and usual care groups, respectively, with no difference in dyspnea scores between treatment groups. There was no difference in the length of stay of the index hospitalization, but the ultrafiltration group had a smaller percentage of patients rehospitalized for heart failure at 90 days (18% and 32%, respectively,  $p=0.037$ ). There were no differences between treatment groups for quality-of-life assessments and renal function, except for a greater likelihood of hypokalemia in the diuretic group ( $p=0.018$ ). An additional subgroup analysis compared the outcomes of the ultrafiltration group versus standard intravenous diuretics by continuous infusion or bolus injection. (6) Similar fluid loss was observed with ultrafiltration and continuous diuretic infusion, with similar outcomes to the original UNLOAD trial, that being fewer rehospitalizations for heart failure at 90 days only in patients who underwent ultrafiltration.

Detailed analysis of the UNLOAD study raises several methodologic concerns that could influence study results. The publication provided insufficient detail of patient status during the study. The authors reported that 20 patients died during the study (9 in the ultrafiltration group, 11 in the usual care group), but the timing of deaths was not reported. The study results, as reported, also raise concerns about dropout rates and patient follow-up for various outcome measures. For example, although 100 patients were randomly assigned to each group, at 48 hours, only 83, 80, and 69 patients in the ultrafiltration group and 84, 83, and 75 patients in the standard care group were reported in the assessment of the 3 primary outcomes (weight loss, dyspnea score, change in serum creatinine level, respectively). For readmission at 90 days, while the denominators are reported as 89 for the treatment group and 87 for the usual care group, information from the report lists 45 and 41 patients at risk, respectively, at 90 days. In addition, it is not clear from the methods that intention-to-treat analyses were performed; and, despite the many outcomes under study, there appears to be no statistical correction for multiple comparisons. Finally, neither participants nor investigators were blinded to treatment, which is a potential source of bias in outcomes such as rehospitalizations, which are clinically based decisions.

In a small substudy from the UNLOAD trial, Rogers et al evaluated the consequences of ultrafiltration and standard intravenous diuretic (furosemide) therapy on glomerular filtration rate (GFR) and renal plasma flow in patients with acute decompensated heart failure.(7) In this study, patients hospitalized for acute decompensated heart failure with an ejection fraction less than 40% and 2 or more signs of hypervolemia were randomly assigned to receive ultrafiltration or intravenous diuretics. Urine output, GFR (as measured by iothalamate), and renal plasma flow (as measured by para-aminohippurate) were assessed before fluid removal and after 48 hours. For the 19 of 25 randomly assigned patients who completed the study (average age, 59 years, 68% male), 9 received ultrafiltration and 10 received intravenous diuretics. The change in GFR (-3.4 mL/min vs -3.6 mL/min), renal plasma flow (26.6 mL/min vs 16.1 mL/min), and filtration fraction (-6.9 mL/min vs -3.9 mL/min) after treatment were not significantly different between the ultrafiltration and furosemide treatment groups, respectively, in this small sample. There was no significant difference in net 48-hour fluid removal between the groups (-3211 mL for ultrafiltration, -725 mL for furosemide, respectively,  $p=0.682$ ). Urine output during 48 hours was significantly greater in the furosemide group. The authors concluded that during a 48-hour period, ultrafiltration did not cause any significant differences in renal hemodynamics compared with the standard treatment of intravenous diuretics.

CARRESS trial. Bart et al reported a randomized trial of 188 patients hospitalized with acute decompensated heart failure which compared ultrafiltration with diuretic-based stepped pharmacologic therapy.(8) Patients participating in the study also had decreased renal function (serum creatinine  $\geq 0.3$  mg/dL) within 12 weeks before or up to 10 days after hospitalization for heart failure. Primary outcomes were changes in serum creatinine and body weight, as measured 96 hours after randomization. The ultrafiltration group experienced a significant increase in serum creatinine levels ( $0.23 \pm 0.70$  mg/dL) compared with the pharmacologic therapy group which had a decrease in serum creatinine levels ( $0.04 \pm 0.53$  mg/dL;  $p=0.003$ ). Mean weight loss was not significantly different between groups ( $5.5 \pm 5.1$  kg [ $12.1 \pm 11.3$  lb] in the pharmacologic therapy group vs  $5.7 \pm 3.9$  kg [ $12.6 \pm 8.5$  lb] in the ultrafiltration group;  $p=0.58$ ). Serious adverse events occurred more frequently in the ultrafiltration group during the 60-day follow-up period compared with the pharmacologic therapy group (72% vs 57%, respectively,  $p=0.03$ ). Serious adverse events included kidney failure, bleeding complications, and complications related to intravenous catheters.

CUORE trial. Marenzi et al reported on a randomized trial of 56 consecutively hospitalized heart failure patients without severe renal insufficiency who were treated with ultrafiltration ( $n=27$ ) or standard medical therapy ( $n=29$ ). (9) All patients had left ventricular ejection fraction of 40% or less and fluid overload of 4 kg or more of recent weight gain and were partially responsive to diuretic therapy. The primary end point was the incidence of heart failure related rehospitalizations during the 1 year after treatment. Four rehospitalizations occurred in the ultrafiltration group, which was significantly lower than the 30 rehospitalizations that occurred in the control group (hazard ratio, 0.14; 95% confidence interval, 0.04 to 0.48;  $p=0.002$ ). In the 1-year follow-up, in the ultrafiltration group, there were 7 deaths (26%) versus 11 (38%) in the control group ( $p=0.33$ ). Weight loss at discharge was similar in both groups ( $p=0.75$ ).

RAPID-CHF trial. Bart et al reported on a small randomized trial involving 40 hospitalized patients with heart failure that investigated safety and efficacy, in which an 8-hour ultrafiltration session with usual care was compared with usual care alone.(10) The primary end point was weight (fluid) loss after 24 hours. Weight loss was 2.5 kg in the experimental group and 1.86 kg in the

usual care group ( $p=0.24$ ); differences in fluid removal (4650 mL vs 2838 mL, respectively) were statistically significant ( $p=0.001$ ).

Badawy and Fahmy. This was an RCT of 40 patients with heart failure in Egypt.(11) Patients were randomized to 72 hours of ultrafiltration versus diuretics. Weight loss and total fluid output were greater in the ultrafiltration group, and length of stay in the intensive care unit (ICU) was less for the ultrafiltration group. There were no significant differences between groups in 30-day mortality, cardiac output, or stroke volume.

Hanna et al. This single-center study from the U.S. evaluated 36 patients with advanced heart failure admitted to the ICU.(12) Patients were randomized to ultrafiltration or conventional care. The primary end point was the time required for the pulmonary capillary wedge pressure to be maintained at 18 mm Hg or lower for 4 consecutive hours, and there was no significant difference on this end point between groups. There were also no significant differences in kidney function, cardiac biomarkers, or adverse events. The ultrafiltration group had a significantly greater weight reduction, a higher total volume of fluid removed, and a shorter length of stay.

ULTRADISCO study. The Effects of Ultrafiltration versus Diuretics on clinical, biohumoral, and hemodynamic variables in patients with decompensated heart failure (ULTRADISCO) study randomized 30 patients to ultrafiltration or diuretics.(13) There was improvement for the ultrafiltration group on a number of hemodynamic measures, including cardiac index, stroke volume index, cardiac power output, cardiac efficiency, and systemic vascular resistance. There were no significant differences between groups on symptom scores, New York Heart Association class, amount of fluid removed, or creatinine levels.

#### Nonrandomized Comparative Studies

A study by Jaski et al compared short- and long-term outcomes, results, and risk profiles from 100 consecutive patients with cardiovascular disorders and recognized pulmonary and systemic volume overload treated with a simplified ultrafiltration system with findings reported from the Acute Decompensated Heart Failure National Registry (ADHERE).(14) Over 43 months, 100 patients (76 men/24 women; age,  $65\pm 14.0$  years; systolic dysfunction, 64%) were treated with ultrafiltration at the discretion of the attending physician during 130 hospitalizations. By using ultrafiltration,  $7.1\pm 3.9$  L of ultrafiltrate was removed during  $2.0\pm 1.2$  treatments per hospitalization. In hospitalizations with a principal diagnosis of heart failure ( $n=79$ ), in-hospital mortality was 7.6% compared with an ADHERE estimated mortality of 7.5%.

#### Case Series

Numerous case series report on outcomes of ultrafiltration, but these studies do not provide useful information on the comparative efficacy of ultrafiltration with conventional management. Examples of some of these case series are described next.

Dev et al analyzed data from a cohort of 72 heart failure patients who received ultrafiltration therapy after inadequate response to medical therapy.(15) While body weight decreased and fluid removal increased significantly with ultrafiltration, renal function deteriorated. In 43% of patients, a 20% or more decrease in the estimated GFR was seen. Dialysis was required in 10% of patients and 13% died. Patarroyo et al found no improvement in renal function in 63 consecutive acute decompensated heart failure patients treated with slow continuous ultrafiltration.(16) Serum creatinine levels were  $2.2\pm 0.9$  mg/dL on admission versus  $2.4\pm 1$  mg/dL after slow continuous

ultrafiltration ( $p=0.12$ ). Conversion to continuous hemodialysis occurred in 59% of patients while 14% were dialysis-dependent on discharge and 30% died during hospitalization.

A study by Giglioli et al from Italy compared hemodynamic parameters in 15 patients before and after slow continuous ultrafiltration (SCUF).<sup>(17)</sup> The authors were able to demonstrate a significant inverse relationship between volumes of fluid removed utilizing this SCUF method and clinical measures of weight (-7.4%,  $p<0.01$ ), edema and dyspnea, diuretic resistance, and plasma brain natriuretic peptide levels ( $21,810\pm 13,016$  to  $8581\pm 5549$ ,  $p<0.01$ ). Dahle et al reported results in 9 patients with acute decompensated heart failure.<sup>(18)</sup> They used a “portable” machine with peripheral intravenous catheters that did not require dialysis or ICU stay. The mean length of time for ultrafiltration was 33 hours, with removal of a mean volume of 7.0 liters and mean weight loss of 6.2 kg. Researchers in Italy published a case series on a wearable device on humans.<sup>(19)</sup> Six subjects with volume overload were treated for 6 hours with the novel system. Fluid removal rate ranged from 116 mL/h to 288 mL/h, at an overall average blood flow rate of 116 mL/min. Sodium removal averaged 151 mmol over the 6 hours. Each patient in the study maintained cardiovascular stability. The authors speculate that a device designed to operate continuously at a slower hourly rate would avoid the cardiovascular instability that requires monitoring and could have an impact on outcomes.

### Ongoing Clinical Trials

A search of online site ClinicalTrials.gov on May 25, 2013, identified 1 phase 4 ongoing study incorporating ultrafiltration in heart failure patients. In the Tolvaptan/Ultrafiltration in the Treatment of Acute Heart Failure (TUF) study, 45 patients will be randomized to usual care, usual care plus tolvaptan or ultrafiltration (NCT01863511). The largest study, the AVOID-HF (Aquapheresis versus Intravenous Diuretics and Hospitalizations for Heart Failure) trial, was terminated early due to patient recruitment challenges (NCT01474200). In this randomized trial, ultrafiltration was to be compared with intravenous diuretics in 810 patients at 40 sites in the U.S.

### Summary

Ultrafiltration is a technique being evaluated for removal of excess fluid from patients with volume overload and heart failure. Ultrafiltration removes fluid from the blood by using pressure differentials with dialysis equipment or similar filtration devices.

The evidence on ultrafiltration for refractory heart failure is insufficient to form conclusions on whether health outcomes are improved. Several randomized studies report improvements on physiologic measures, and some report reductions in ICU stay and/or readmissions for heart failure. However, these trials do not demonstrate improvement on relevant clinical outcomes, and the improvements in physiologic parameters and utilization measures are not consistent across studies. Additionally, there have been reports of significant worsening of renal function and serious adverse events following ultrafiltration in acute heart failure patients. Further study is warranted to identify whether there may be appropriate patient groups for ultrafiltration and to define patient selection criteria. Finally, there are some methodologic limitations in the available trials, and the outcomes reported are short to medium term. For these reasons, the use of ultrafiltration for refractory heart failure is considered investigational.

### Practice Guidelines and Position Statements

Consensus statements give limited recommendations regarding the clinical value of ultrafiltration in the treatment of patients with heart failure. The Heart Failure Society of America’s (HFSA) 2010

Comprehensive Heart Failure Practice Guidelines indicate ultrafiltration may be considered for the treatment of acute decompensated heart failure fluid overload in lieu of diuretics. (Level B evidence- cohort or smaller studies) The HFSA guidelines also indicate ultrafiltration may be considered when congestion continues despite diuretic therapy (Level C evidence - opinion).(20) The European Society of Cardiology Task Force's 2012 guidelines on the diagnosis and treatment of acute heart failure states "ultrafiltration is sometimes used to remove fluid in patients with HF, although is usually reserved for those unresponsive or resistant to diuretics."(21) The guidelines noted, however, the efficacy and safety of ultrafiltration is unknown. The 2013 ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults (under Recommendations for Hospitalized Patient) lists ultrafiltration as a Class IIb recommendation (benefit greater than or equal to risk, additional studies needed).(22) The recommendations state ultrafiltration "may be considered for patients with obvious volume overload to alleviate congestive symptoms and fluid weight" (Level of Evidence B: conflicting evidence) and "for patients with refractory congestion not responding to medical therapy" (Level of Evidence C: recommendation less well established).

## **CODING**

**The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.**

### CPT/HCPCS

37799 Unlisted procedure, vascular surgery  
90999 Unlisted dialysis procedure, inpatient or outpatient

- There are no specific CPT codes for this procedure.
- There is an ICD-9-CM procedure code specific to the procedure: 99.78 Aquapheresis

### DIAGNOSES

Experimental / Investigational for all diagnoses related to this medical policy.

## **REVISIONS**

04-08-2012	Policy added to the bcbsks.com web site.
10-31-2013	Description section reviewed
	Rationale section updated
	References updated
09-03-2014	In Policy section: <ul style="list-style-type: none"> <li>▪ Revised the policy statement to add "compensated" and "who are being treated in the outpatient setting" to read, "The use of ultrafiltration is considered experimental / investigational in patients with compensated congestive heart failure who are being treated in the outpatient setting."</li> </ul>
	Rationale section updated
	References updated

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