Name of Policy: 
Ultrafiltration in Decompensated Heart Failure

Policy #: 435                                Latest Review Date: June 2014
Category: Medicine                            Policy Grade: A

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
Description of Procedure or Service:
Ultrafiltration is a technique being evaluated for removal of excess fluid from patient with volume overload and heart failure. Ultrafiltration removes fluid from the blood by using pressure differentials with dialysis equipment or similar filtration devices.

Congestive heart failure is a relatively common problem and frequently results in hospitalizations and readmissions. Various approaches are being explored in treating these patients, especially those who are refractory (unresponsive) to conventional therapy. Ultrafiltration is one technique receiving increasing notice for a possible role in hospitalized patients with marked volume overload from congestive heart failure. Ultrafiltration is a process 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 some recent studies, this technique is also referred to as Aquapheresis. Work is also beginning on newer devices that allow for continuous ultrafiltration in ambulatory patients. For example, in 2006 researchers at UCLA reported on use of a continuous device in animals.

Policy:
The use of ultrafiltration does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage in patients with heart failure and is considered investigational.

This policy does not apply to patients with renal failure being treated using dialysis.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the members' contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:
The most recent literature review is through May 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 to comparable groups receiving conventional treatment. Since 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 one 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 two meta-analyses) of RCTs have been published. All of the reviews found ultrafiltration resulted in significantly greater weight loss and fluid removal than diuretic therapy. Three reviews found no significant differences in adverse events, and one found the evidence to be inconclusive. Two reviews reported on all-cause mortality and re-hospitalizations and found no significant differences between ultrafiltration and diuresis. Additionally, one review found no significant differences in dyspnea score or increase in creatinine levels. Limitations reported in the review included small studies sizes and publication biases.

Randomized, controlled trials
UNLOAD trial
The UNLOAD trial was a non-blinded 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). The study was conducted during one year at 28 U.S. centers. Primary efficacy endpoints were 48-hour weight loss and dyspnea score (1–7 Likert scale). Primary safety endpoints 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 endpoints 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 (IV) diuretics by continuous infusion or bolus injection. Similar fluid loss was observed with ultrafiltration and continuous diuretic infusion; with similar outcomes to the original UNLOAD trial that being fewer re-hospitalizations 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 (nine in the ultrafiltration group and 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 three primary outcomes (weight loss, dyspnea score, and 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, in spite of 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 re-hospitalizations, which are clinically based decisions.

In a small sub-study 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. In this study, patients hospitalized for acute decompensated heart failure with an ejection fraction less than 40% and two 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 was 59 years, 68% were male), nine received ultrafiltration and ten 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 (-3,211 mL for ultrafiltration and -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. Patients participating in the study also had decreased renal function (serum creatinine ≥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±0.70 mg/dL) compared with the pharmacologic therapy group which had a decrease in serum creatinine levels (0.04±0.53 mg/dL; p=0.003)). Mean weight loss was not significantly different between groups (5.5±5.1 kg [12.1±11.3 lb] in the pharmacologic therapy group vs 5.7±3.9 kg [12.6±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). 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 re-hospitalizations during the one year after treatment. Four re-hospitalizations occurred in the ultrafiltration group, which was significantly lower than the 30 re-hospitalizations that occurred in the control group (hazard ratio, 0.14; 95% confidence interval, 0.04 to 0.48; p=0.002). In the one-year follow-up, in the ultrafiltration group, there were seven 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 eight hour ultrafiltration session with usual care was compared to usual care alone. The primary endpoint 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 (4,650 mL vs. 2,838 mL, respectively) were statistically significant (p=0.001).

**Badawy and Fahmy**

This was an RCT of 40 patients with heart failure in Egypt. 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. Patients were randomized to ultrafiltration or conventional care. The primary endpoint was the time required for the pulmonary capillary wedge pressure to be maintained at 18 mm Hg or lower for four consecutive hours, and there was no significant difference on this endpoint 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, bio-humoral and hemodynamic variables in patients with decompensated heart failure (ULTRADISCO) study randomized 30 patients to ultrafiltration or diuretics. 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 (NYHA) class, amount of fluid removed, or creatinine levels.

**Non-randomized, 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). Over a period of 43 months, 100 patients (76 men/24 women, 65 +/- 14.0 years of age, systolic dysfunction 64%) were treated with ultrafiltration at the discretion of the attending physician during 130 hospitalizations. By using ultrafiltration, 7.1 +/- 3.9 L of ultrafiltrate were removed during 2.0 +/- 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 below.

A study by Giglioli et al from Italy compared hemodynamic parameters in 15 patients before and after slow continuous ultrafiltration (SCUF). 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 (BNP) levels (21,810 +/- 13,016 to 8,581 +/- 5,549, p <0.01). Dahle et al reported results in nine patients with acute decompensated heart failure. They used a “portable” machine with peripheral intravenous catheters that did not require dialysis or intensive care unit 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. Six subjects with volume overload were treated for six 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 six 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.

**Summary**
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, the available trials have methodologic limitations, 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 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) The European Society of Cardiology Task Force's 2012 guidelines on the diagnosis and treatment of acute heart failure stated that ultrafiltration is sometimes used to remove fluid in patients with HF, although is usually reserved for those unresponsive or resistant to diuretics.” 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). 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).

**Key Words:**
Ultrafiltration, Aquapheresis, Aquadex, FlexFlow, CHF Solutions

**Approved by Governing Bodies:**
In June 2002, the “Aquadex™ FlexFlow™ System” (CHF Solutions) was cleared for marketing by the 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 some modifications.

The FDA determined that this device was substantially equivalent to existing devices for use in temporary (up to eight hours) ultrafiltration treatment of patients with fluid overload who have failed diuretic therapy, and for extended (longer than eight hours) ultrafiltration treatment of patients with fluid overload who have failed diuretic therapy and require hospitalization.

**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply  
FEP: FEP does not consider investigational if FDA approved. Will be reviewed for medical necessity.  
Pre-certification requirements: Not applicable
Coding:
CPT Codes: There are no specific CPT codes for this procedure

References:
20. McMurray JJ, Adamopoulos S, Anker SD et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012; 33(14):1787-847.

Policy History:
Medical Policy Group, December 2006 (2)
Medical Policy Panel, June 2008
Medical Policy Panel, June 2010
Medical Policy Group, June 2010 (2)
Medical Policy Administration Committee, June 2010
Available for comment June 18-August 2, 2010
Medical Policy Group, January 2012 (3): Updated Key Points and References-added
Medical Policy Panel, June 2012
Medical Policy Group, July 2012 (4): Updated Key Points and References
Medical Policy Group, September 2013 (4): 2013 Update to Key Points and References
Medical Policy Group, October 2013 (4): Removed ICD-9 Procedure codes; no change to policy statement.
Medical Policy Panel, June 2014
Medical Policy Group, June 2014 (4): Updated Key Points and References. No change to the policy statement.

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.