APPENDIX to Ultrafiltration in Decompensated Heart Failure Policy

Prior Authorization Requirements

This service (or procedure) is considered **investigational** in all instances. If you would like to submit additional information please forward to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

Evidence Basis for the Policy

Rationale

Congestive heart failure (CHF) is a relatively common problem and frequently results in hospitalizations and readmissions. Various approaches have been explored in treating refractory congestion (fluid overload) that is unresponsive to conventional therapy (e.g., intravenous (IV) furosemide (Lasix®), angiotensin converting enzymes (ACEs), angiotensin receptor blockers (ARBs), IV inotropes, and beta-blockers). Ultrafiltration has received increased interest primarily in the hospital setting and specialized dialysis units for the treatment of patients with marked volume overload from CHF.

In ultrafiltration therapy, “blood is withdrawn from the body, pumped through a filter, and returned to the body. The pump produces a pressure gradient across a semi-permeable membrane, which expels an isotonic solution of water and salts from the blood, before returning the filtered blood to the patient.” (Hayes, 2007). Ultrafiltration differs from hemodialysis in that it does not remove toxins and does not act via diffusion. Conventional ultrafiltration is performed with hemodialysis machines requiring central venous access with a double lumen catheter. Monitoring is provided by dialysis technicians in specialized hospital units. Newer portable systems have been developed using peripheral catheters and lower blood flow rates allowing ultrafiltration in a variety of patient settings. Work has also begun on newer devices that allow

continuous ultrafiltration in ambulatory patients (Gura et al., 2006). Newer systems allow fluid removal of up to five liters of excess fluid in a single four- to nine-hour treatment (Hayes, 2007).

In June 2002, the Aquadex™ FlexFlow™ System (CHF Solutions, Brooklyn Park, MN) was cleared for marketing by the United States Food and Drug Administration (FDA) through the 510(k) process. The Aquadex™ received numerous supplemental 510(k) approvals (classified as a high permeability dialysis system) for modifications and extended use (longer than eight hours). The current approved FDA indications for use of this system are:

- Temporary (up to eight hours) ultrafiltration treatment of patients with fluid overload who have failed diuretic therapy
- Extended (longer than eight hours) ultrafiltration treatments of patients with fluid overload who have failed diuretic therapy and require hospitalization

Treatments are to be prescribed by a physician, and administered by health care providers whom have received training in extracorporeal therapies (FDA, 2007).

The NxStage System One™ (NxStage Medical Inc., Lawrence, Massachusetts), FDA approved in July of 2003, is indicated for hemodialysis and/or ultrafiltration in acute or chronic care facilities or at home. NxStage System One™ also received various approvals for modifications to components, labeling, and to extend its indication to home use (Hayes, 2007).

In evaluating this technology, the primary question is whether ultrafiltration improves important health outcomes. While removal of fluid and sodium (and weight) is important, these are viewed as surrogate outcomes. Information is required regarding 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.

Bart and colleagues (2005) 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 end point was weight (fluid) loss after 24 hours. Weight loss was 2.5 kilograms (kg) in the experimental group and 1.86 kg in the usual care group ($p = 0.24$); differences in fluid removal (4,650 milliliters (mL) versus 2,838 mL, respectively) were statistically significant ($p = 0.001$).

Costanzo and colleagues (2005) reported results on use of ultrafiltration before diuretics in 20 patients with heart failure and diuretic resistance. They found both volume reduction and weight loss. They also indicated that length of hospital stay was reduced.

Dahle and colleagues (2006) 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 seven liters and mean weight loss of 6.2 kg.

Results of a larger randomized study, the UNLOAD (ultrafiltration versus diuretics for patients hospitalized for acute decompensated congestive heart failure) clinical trial involved 200 patients hospitalized for heart failure and hypervolemia randomly assigned during the first 24 hours of

hospitalization to ultrafiltration or usual care (diuretics) (Costanzo et al., 2007). The study was conducted during one year at 28 centers. Primary efficacy end points were 48-hour weight loss and dyspnea score (1 to 7 Likert scale). 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 ($p = 0.018$).

Given the overall prevalence of heart failure, new treatments must be based on large trials using rigorous methodology and analyses. Detailed analysis of this study raises several methodological concerns that could influence study results. The publication provided insufficient detail of patient status during the study. The authors reported 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 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 listed 45 and 41 patients at risk 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 rehospitalizations, which are clinically based decisions. Given these concerns, the findings from this study must be viewed as preliminary and thus do not substantially contribute to the understanding of long-term clinical outcomes of ultrafiltration as a treatment for decompensated heart failure.

A Hayes Technology Brief (2007, update 2009), reported definitive conclusions on the efficacy of this treatment requires “independent replication of results preferably in large, double-blind studies with cost-effectiveness evaluations and much longer follow-up, to determine if outcomes reported for ultrafiltration to date translate into real patient benefits and/or cost-savings over the long term.”

In a small sub-study from the UNLOAD trial, Rogers et al., (2008) evaluated the consequences of ultrafiltration and standard intravenous diuretic (furosemide) therapy on glomerular filtration rate 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. For the 19 of 25 randomly assigned patients who completed the study (average age was 59 years, 68% were male), nine received ultrafiltration and 10 received IV diuretics. 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.

A study by Jaski et al., (2008) 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 were treated with ultrafiltration at the discretion of the attending physician during 130 hospitalizations. The authors concluded that this series extends the spectrum of patients previously reported to be treated with ultrafiltration. Despite marked volume overload, ultrafiltration-treated patients with a principal diagnosis of heart failure had inpatient outcomes similar to those of the ADHERE registry. However, conclusions regarding the efficacy of ultrafiltration in the volume-overloaded patients in this study are limited by comparison with database information rather than a contemporaneous control group. In addition, patient selection criterion for applying ultrafiltration was not prespecified.

In 2008, researchers in Italy published a case series on a wearable device for humans. Six subjects with volume overload were treated for six hours with the novel system. Fluid removal rate ranged from 116 mL/hour to 288 mL/hour, at an overall average blood flow rate of 116 mL/minute. Each patient in the study maintained cardiovascular stability (Ronco et al., 2008). The authors speculated 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.

The European Society of Cardiology Task Force's guidelines on the diagnosis and treatment of acute heart failure stated ultrafiltration should be considered to reduce fluid overload in selected patients, and to correct hyponatremia in symptomatic patients who are refractory to diuretics (Dickstein et al., 2008). The guidelines noted, however, the appropriate selection criteria for ultrafiltration have not been established.

The 2009 American College of Cardiology Foundation (ACCF) / American Heart Association (AHA) Guidelines for the Diagnosis and Management of Heart Failure in Adults (under Recommendations for Hospitalized Patient) lists ultrafiltration as a Class IIa recommendation (benefit greater than risk, additional studies needed) and a Level of Evidence of B (conflicting evidence) (Jessup et al., 2009). The recommendation states “Ultrafiltration is reasonable for patients with refractory congestion not responding to medical therapy.”

A study by Giglioli et al., (2010) from Italy compared hemodynamic parameters in 15 patients before and after slow continuous ultrafiltration (SCUF). Each patient was New York Heart Association (NYHA) class III or IV at the onset of treatment. Hemodynamic parameters were measured using a pressure recording analytical method (PRAM), described as a minimally invasive monitor in the radial artery. 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, $p < 0.01$). Secondary end points of hemodynamic measures utilizing PRAM monitor were observed to correlate positively in cardiac output, contractile cardiac efficiency, and reduced systemic vascular resistance. Given the small study size, lack of control group, and a focus on the unique hemodynamic measures of PRAM, this study does not lead to a change in the policy statement.

In summary, published evidence to evaluate the impact of ultrafiltration on important clinical outcomes is limited. The published clinical trials involve small patient populations and report short-term to intermediate outcomes. Ninety-day readmission appear to be reduced in the

ultrafiltration group in one study (UNLOAD trial), but otherwise no studies to date address long-term mortality or morbidity, or quality of life outcomes. Clinical trials currently underway may provide information that the existing body of evidence does not possess (clinicaltrials.gov, 2010). Therefore, given the uncertain impact on health outcomes, this procedure is considered investigational.

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. 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.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA) - approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

Type	Number	Description
CPT	None	
HCPC	None	
ICD9 Procedure	99.78	Aquapheresis
ICD9 Diagnosis	All Diagnoses	
Place of Service	All Places of Service	

Tables

N/A

Definitions

Aquapheresis - A medical therapy designed to remove excess salt and water from the body from patients suffering from fluid overload.

Heart failure (congestive heart failure) - A clinical syndrome characterized by systemic perfusion inadequate to meet the body's metabolic demands as a result of impaired cardiac pump function.

Hemodialysis - The process of removing specific small molecules (e.g., uric acid) from a solution (e.g., blood) by letting them diffuse across a semipermeable membrane into water. It is a mechanical process that performs part of the work that healthy kidneys normally do. The main functions of dialysis include clearing wastes from the blood, restoring proper balance of certain electrolytes in the blood, and eliminating extra fluid from the body.

Ultrafiltration - Filtration (separation) through a medium (i.e., semipermeable capillary wall) which allows small molecules (i.e., water) to pass but holds back larger ones (i.e., protein). In ultrafiltration the separation is accomplished by convective (movement of molecules within fluids) transport.

Index / Cross Reference of Related BSC Medical Policies

The following Medical Policies share diagnoses and/or are equivalent BSC Medical Policies:

N/A

Key / Related Searchable Words

N/A

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Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
10/15/2007	Adopted CTAF (06/07) and BCBSA MPP (12/06)	Medical Policy Committee
1/7/2011	Policy revision without position change	Medical Policy Committee

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.

Click here to view the policy statement for this policy

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