Centre universitaire de santé McGill
McGill University Health Centre

Technology Assessment Unit of the McGill University Health Centre

Efficacy, safety and cost of ultrafiltration for the management of acute decompensated heart failure

Report Number 47

May 31, 2010

Report available at **www.mcgill.ca/tau/**

Report prepared for the Technology Assessment Unit (TAU)
of the McGill University Health Centre (MUHC)

by

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Invitation.
This document was developed to assist decision-making in the McGill University Health Centre. All are welcome to make use of it. However, to help us estimate its impact, it would be deeply appreciated if potential users could inform us whether it has influenced policy decisions in any way.
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ACKNOWLEDGEMENTS

The expert assistance of the following individuals is gratefully acknowledged:

- Dr. Viviane Nguyen

  Director, Coronary Care Unit (CCU), Cardiovascular Division, MUHC.

- Mr Alain Lapointe

  External Consultant – French Translation

TIMELINES

Report requested on February 24, 2010, by Mr. Gary Stoopler, Administrative Director, Surgery, Medicine, Cancer Care, Mental Health & Women's Health, MUHC

Commenced: February 25, 2010

Completed: May 31, 2010

DEFINITIONS

The following terms are frequently used without precision. In this report we will use the following definitions:

- Heart failure – A clinical syndrome resulting from the inability of the heart to pump sufficient blood to meet the metabolic demands of the body.
- Acute heart failure – Heart failure of recent onset.
- Decompensated heart failure – Failure of the body's homeostatic mechanisms to successfully compensate for the inadequate blood supply resulting from heart failure.
- Cardio renal syndrome – Evidence of renal insufficiency resulting from heart failure (Increase in serum creatinine of > 0.3 mg per decilitre from baseline).
- Diuretic resistant – Absent or reduced diuresis in response to increased dosage.

ABBREVIATIONS

Agence	Agence de la santé et des services sociaux de Montréal
HTA	Health Technology Assessment
NHS CEP	National Health Service Centre for Evidence-based Purchasing
RQCT	Réseau québécois de cardiologie tertiaire
MUHC	McGill University Health Centre
UF	Ultrafiltration

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PRINCIPAL MESSAGES

- Ultrafiltration is effective for the management of severe heart failure and the method of choice when patients have become resistant to diuretics.

- Net budget impact of treating 50 diuretic resistant cases by UF instead of standard care is uncertain. Probably in the order of $20,000 per year, (but possibly $107,000, or -$76,000).

- Possible but unproven long-term health benefits include reduced re-hospitalization.

- It is recommended that budget should be provided for UF management of diuretic resistant heart failure and that the cardiovascular division undertake a study to identify the extent and duration of health benefits of UF. At present it should not be used in the absence of diuretic resistance.

EXECUTIVE SUMMARY

Background

Ultrafiltration is increasingly used for the management of acute decompensated heart failure. Its exact role is not yet clearly defined. The cardiology division of the McGill University Health Centre (MUHC) has submitted an application to use this therapeutic approach for 50 patients per year suffering from acute, decompensated, diuretic-resistant heart failure in the cardiology intensive care unit.

Objective

Evaluate the evidence of the efficacy, safety, and cost of the proposed intervention.

Methods

A literature search was carried out, searching for systematic reviews, health technology assessments, and randomized controlled trials of ultrafiltration for heart failure, between January 1993 and April 2010.

Results

Two recent HTA reports concluded that ultrafiltration effectively treats patients with decompensated heart failure by removing excessive fluids. We identified five randomized controlled trials. All studies reported effective fluid removal. There was no evidence of shorter length of hospital stay in patients treated by ultrafiltration compared to standard care. There is some evidence that there are long-term health benefits following ultrafiltration compared to diuretics. In one study of 200 patients the rate of re-admission was reported to be roughly 15% less after treatment of ultrafiltration.

Budget Impact at the MUHC

The anticipated budget impact of the proposed use of UF at the MUHC will depend on several factors such as the duration of hospital stay, and the rate and duration of hospital re-admissions associated with standard care and UF for which data do not exist. However, on the basis of a series of assumptions, the estimated cost per treatment of UF and standard

intravenous diuretics is $6,606 and $6,193, respectively. Thus, the costs of treating 50 patients with diuretic resistant heart failure per year are as follows:

- Ultrafiltration- $330,318 (95% CI, $282,196 - $410,635)
- Standard Care - $309,644 (95% CI, $262,594 - $400,209)
- Thus, treatment of 50 patients by UF who would otherwise receive standard care would result in a budget impact of: $330,318 - $309,644 = $20,674 per year (95% CI, -$76,091 to $107,199)

CONCLUSIONS

- **There is sufficient evidence to conclude that ultrafiltration is an effective technology for the management of acutely decompensated heart failure.**

- **UF is the method of choice when patients have become resistant to diuretics or have developed secondary renal failure.**

- **On the basis of several assumptions for which the evidence is insubstantial, it is estimated that the cost of treating 50 diuretic resistant cases by UF instead of standard care, might have a net budget impact of $20,000 per year. [Note however, that this estimate is uncertain. The annual budget impact might be as great as $107,000, or there might be a savings of up to $76,000.]**

- **There is limited evidence that ultrafiltration may have long-term health benefits including improved exercise performance for up to three, and possibly six months, and that these effects are associated with a reduction in rehospitalization rates.**

RECOMMENDATIONS

- **UF treatment should be available for the management of the estimated 50 diuretic resistant heart failure patients per year in the MUHC. It is recommended that budget be made available for this purpose.**

- **It is recommended that the cardiovascular division undertake a study to identify the extent and duration of the health benefits of UF**.

- **Until there is clear evidence of long-term benefit (probably with an associated reduction in hospital costs), UF should not be used for the treatment of heart failure in the absence of diuretic resistance.**

SOMMAIRE

Contexte

L'ultrafiltration est de plus en plus utilisée lors de défaillance cardiaque aigue, mais son rôle thérapeutique n'est pas très bien défini. Le service de cardiologie du CUSM (Centre universitaire de santé McGill) a soumis une demande pour utiliser cette approche thérapeutique à l'unité des soins intensifs chez 50 patients par année souffrant de défaillance cardiaque aigue et résistants aux diurétiques.

Objectif

L'objectif de ce rapport est d'évaluer les preuves de cette approche en regard de l'efficacité, de l'innocuité et des coûts impliqués.

Méthodologie

Une revue de la littérature fut menée pour identifier les revues systématiques, les évaluations technologiques (HTA) ainsi que les études randomisées traitant de l'utilisation de l'ultrafiltration lors de défaillance cardiaque, entre les mois de janvier 1993 et avril 2010.

Résultats

Deux rapports d'évaluation des technologies récents conclurent que l'ultrafiltration traite efficacement les patients souffrant de défaillance cardiaque en éliminant les fluides excédentaires. Cinq études randomisées furent aussi identifiées et toutes rapportaient une élimination efficace des fluides. Aucune évidence ne montrait une diminution de la durée d'hospitalization chez les patients traités avec ultrafiltration par rapport à la thérapie classique. Il existe quelques évidences montrant des effets positifs sur la santé à long terme suivant l'ultrafiltration, comparée à l'approche diurétique. Une étude impliquant 200 patients rapporta une diminution du taux de réadmission de 15% après traitement par ultrafiltration.

Impact budgétaire au CUSM

L'impact budgétaire de l'utilisation de l'ultrafiltration au CUSM dépendra de plusieurs facteurs tels la durée d'hospitalization, le taux et la durée de réadmission pour la thérapie classique et

pour l'ultrafiltration pour laquelle il n'existe aucune donnée. Cependant, à partir de certaines hypothèses de travail, l'évaluation des coûts pour un traitement par ultrafiltration et par diurétiques intraveineux est de 6 606 $ et 6 193 $, respectivement. Les coûts pour traiter annuellement 50 patients résistants aux diurétiques sont donc les suivants :

- Ultrafiltration – 330 318 $ (95% CI, 282 196 $ - 410 635 $)
- Traitement classique – 309 644 $ (95% CI, 262 594 $ - 400 209 $)

Ainsi, le traitement de 50 patients par ultrafiltration, comparativement à l'approche classique, aurait un impact budgétaire annuel de 20 674 $ (95% CI,
-76 091 $ à 107 199 $).

CONCLUSIONS

- **Il existe des preuves suffisantes pour conclure que l'ultrafiltration est une technologie efficace pour le traitement de la défaillance cardiaque aigue.**

- **L'ultrafiltration est la méthode de choix chez les patients résistants aux diurétiques ou qui ont développé une défaillance rénale secondaire.**

- **En se basant sur plusieurs hypothèses pour lesquelles les évidences sont insuffisantes, il est estimé que les coûts pour traiter par ultrafiltration 50 patients résistants aux diurétiques pourraient avoir un impact budgétaire d'environ 20 000 $ par année. Il est à noter que cet estimé est approximatif. L'impact budgétaire annuel pourrait être aussi important que 107 000$ ou pourrait démontrer des économies de l'ordre de 76 000 $.**

- **Il existe des preuves très limitées à l'effet que l'ultrafiltration pourrait avoir à long terme des bénéfices sur la santé, incluant une amélioration de la performance physique jusqu'à trois mois, et possiblement six mois, et que ces effets sont associés à une diminution du taux d'hospitalization.**

RECOMMANDATIONS

- **L'ultrafiltration devrait être disponible au CUSM pour le traitement d'environ 50 patients par année montrant une défaillance cardiaque et résistants aux diurétiques. Il est recommandé qu'un budget soit dégagé à cet effet.**

- **Il est recommandé que le service de cardiologie entreprenne une étude pour identifier l'importance et la durée des bénéfices de l'ultrafiltration sur la santé.**

- **À moins d'évidences précises sur des bénéfices à long terme (probablement associées à une réduction des coûts hospitaliers), l'ultrafiltration ne devrait pas être utilisée pour le traitement de la défaillance cardiaque en l'absence d'une résistance aux diurétiques.**

Efficacy, safety and cost of ultrafiltration for the management of acute decompensated heart failure

INTRODUCTION

Heart failure is a clinical syndrome resulting from the inability of the heart to pump sufficient blood to meet the metabolic demands of the body. A common feature of heart failure is fluid retention, which in turn causes elevation of pressure in the venous system, edema of peripheral tissues and lungs, and an increase in body weight.

Normally, patients diagnosed with heart failure are prescribed oral diuretics, which, at least initially correct fluid overload and relieve symptoms.[1] However, with time, many patients become increasingly resistant to diuretics,[2] a condition that is treated by increasing diuretic dosage. However, eventually 5-10% of such patients become highly unresponsive to diuretics and they require hospitalization with administration of diuretics intravenously. The length of hospitalization for this purpose in Quebec is reported to average 9.7 days.[2]

A new approach to the elimination of excess fluid in heart failure is by use of ultrafiltration (UF). Using either peripheral or central venous access, blood is withdrawn and passed through the ultrafiltration unit where water and electrolytes are removed under negative pressure. The blood is then re-infused into the patient.[3] The fluid removal rate can be adjusted from 120 up to 500 ml/hour.[4] This technology was approved by the FDA in 2002 and has been approved by Health Canada since 2007. Ultrafiltration does not replace dialysis, for it only removes excessive fluid and electrolytes; it does not correct acid/base imbalance, treat hyperkalemia, or remove toxins.[5] Currently, the only apparatus made for this purpose is marketed by Gambro Inc. Two models are available, Aquadex and Prismaflex. The Prismaflex is a multi-functional apparatus that can be used for all types of continuous renal replacement therapy . Aquadex, , the unit requested in the application of the cardiovascular division of the MUHC is a compact, mobile unit used for ultrafiltration only.

Aquadex FlexFlow

Ultrafiltration at the MUHC

Currently, a pilot study of five patients in the outpatient dialysis unit is underway to ensure familiarity with the technology. Thereafter, it is intended to implement peripheral ultrafiltration in the CCU, for 48-72 hours at a time in acutely decompensated heart failure patients, who are diuretic-resistant. There is reason to hope that use of ultrafiltration in such patients, could shorten length of stay and reduce the rate of re-admissions.

Objectives

To carry out a systematic review of the literature to determine:

1. The clinical efficacy of ultrafiltration for the treatment of acute decompensated diuretic-resistant heart failure.
2. To estimate the cost of this technology and the possible budget impact, using likely estimates of its effect on the length of index hospitalization and the frequency of re-hospitalization.

METHODS

A search of existing Health Technology Assessments (HTAs) published since 1990 on ultrafiltration for the treatment of congestive heart failure was performed using the University of York's Centre for Reviews and Dissemination online databases. Medline and EMBASE were searched for relevant randomized controlled trial (RCTs). The bibliographies of published articles were also used. Keywords used included "ultrafiltration OR hemofiltration OR hemodiafiltration," "heart failure," "randomized controlled trial," and "cost." Searches were not limited by language or year of publication.

Data on weight loss, volume of fluid removal, hemodynamic and laboratory outcomes, and adverse events were extracted. In order to estimate the possible budget impact of ultrafiltration, data on the length of index hospital stay and subsequent re-hospitalizations were also collected.

RESULTS OF SYSTEMATIC REVIEW

Four technology assessment reports were identified. One, a technology briefing report, was published in 2006 by the National Horizon Scanning Centre, University of Birmingham, UK.[6] An HTA report published by Hayes Inc., was not retrievable online without purchase. Two recent HTA reports,[2;3] both presented thorough systematic reviews and cost analyses. In addition, two cost-effectiveness analyses were identified.[7;8]

Finally, two randomized controlled trials of UF vs. intensive intravenous diuretic therapy in acute decompensated heart failure, reported in three citations, were identified.[9-11] Two additional studies[12;13] that investigated moderate congestive heart failure were retained. Study size ranged from 200[10] to 16[11] patients. No meta-analysis was performed due to the differences in study methods across the trials.

HTA reports and systematic reviews

A UK review carried out in 2008[3] concluded that ultrafiltration for the treatment of heart failure is at least as effective as intravenous diuretic in terms of fluid removal, and could be used in diuretic-resistant patients. Those treated with ultrafiltration showed a substantial improvement in exercise test performance compared with those treated with diuretics for up to 3 months. It had yet to be determined whether there was a maximum rate of fluid removal that would still avoid complications and adverse events. Their cost analysis indicated that ultrafiltration was more expensive than medical therapy due to the costly consumables. A comprehensive Quebec review completed in October 2008 by the Groupe d'experts en insuffiance cardiaque[2] concluded that ultrafiltration's effectiveness in removing excessive fluid and achieving weight loss was "evident".

Randomized controlled trials

Five reports were identified in which patients were randomized to receive ultrafiltration or diuretic therapy. The objectives, the characteristics of patients, and the methods in each study varied considerably. They are summarized below and in Table 1.

Costanzo 2007[10]

- ***Objectives:*** To compare the safety and efficacy of ultrafiltration and standard intravenous diuretic therapy.
- ***Patient population:*** Acute decompensated heart failure; there is no mention of diuretic resistance in the text.
- ***Methods:*** N=200 patients (multicentre study), with random allocation to 48 hours of ultrafiltration, or 48 hours of intravenous diuretics, at a dose at least twice the before-hospitalization daily oral dose.
- ***Results:*** At 48 hours both weight loss (ultrafiltration 5.0 +/-3.1 kg vs. IV diuretics 3.1 +/-3.5 kg) and net fluid loss (ultrafiltration 4.6 L vs. IV diuretics 3.3 L), were greater with *ultrafiltration, (p=0.001 in each). At 90 days following treatment, there was a lower* re-hospitalization rate following ultrafiltration (18% vs. 32%, p=0.037).
- ***Comment:*** At the dosages used, in these (possibly not diuretic-resistant) cases of "decompensated" heart failure, ultrafiltration had a better short-term result than intravenous diuretic. There was also a lower re-hospitalization rate in the first 90 days. Evaluation was unblinded.

Rogers 2008 [11]

- ***Objectives:*** To evaluate the consequences of ultrafiltration and intravenous diuretic on glomerular filtration rate, and renal plasma flow.
- ***Patient population:*** Acute decompensated heart failure; probably not diuretic resistant (exclusion of previous use of intravenous diuretic).
- ***Method:*** After randomization, 9 patients received ultrafiltration therapy for 48 hours, during which time their diuretic therapy was discontinued, while 10 control patients received intravenous diuretic at a dose that was at least twice the pre-hospitalization daily oral dose.
- ***Results:*** There was no statistically significant difference in the 48-hour fluid removal or in the renal function parameters measured. The 48-hour urine output was significantly less in the ultrafiltration group (2286 +/- 915 mL vs. 5786 +/-2587 mL).

- ***Comment:*** In patients with acute decompensated heart failure who have not become diuretic-resistant, ultrafiltration has no adverse effect on renal function compared to diuretic therapy

Agostoni 1994[12]

- ***Objectives:*** To investigate the relationship of pulmonary fluid accumulation to functional performance, and the response to water unloading.
- ***Patient population:*** Moderate, stable, heart failure, by inference, not diuretic resistant.
- ***Method:*** 16 patients randomly allocated to receive ultrafiltration or an intravenous bolus of supplemental furosemide.
- ***Results:*** The amount of body fluid removed with either intervention was equal, (1600 ml). By three months follow-up, bodyweight of the furosemide group was up by 1 kg and the haemodynamic variables examined had returned to control values. By contrast in the ultrafiltration group, average patient bodyweight was down by 1.5 kg and lung function and exercise capacity were substantially improved.
- ***Comment:*** Patients were in stable moderate heart failure. The acute effects of the two treatments did not differ. However, the improved respiratory and exercise function observed at 3-month following ultrafiltration but not following diuretic, suggests that there may be health effects of ultrafiltration that are not associated with diuresis.

Bart 2008[9]

- ***Objectives:*** To assess the safety and efficacy of ultrafiltration.
- ***Patient population:*** Decompensated congestive heart failure; no mention of severity, acuteness, diuretic resistance, or renal function.
- ***Method:*** Random allocation of 20 patients to a single 8-hour course of ultrafiltration, during which diuretics were withheld, and 20 patients to usual care. Control patients did not receive increased diuretic or intravenous diuretics.
- ***Results:*** Fluid removal by ultrafiltration was 4650 mL, and with usual care 2838 mL, p= 0.001.
- ***Comment:*** These patients were probably not acute, and probably not severe. Ultrafiltration was not compared with stepped-up or intravenous diuretic therapy.

Ultrafiltration was "safe" and removed more fluid than diuretics (given orally at normal, not increased, dosage)

Pepi 1993[13]

- ***Objectives:*** To evaluate whether ultrafiltration is beneficial in patients with moderate congestive heart failure.
- ***Patient population:*** Moderate, stable, heart failure; NYHA class 11 and 111.
- ***Method:*** Random allocation of 36 patients to receive a single session of ultrafiltration or usual treatment (*oral* diuretics *without* increase in dosage).
- ***Results:*** Compared to usual treatment, UF resulted in significantly better lung function and peak oxygen consumption with lower resting norepinephrine levels for up to 180 days.
- ***Comment:*** Patients were in mild to moderate, stable, cardiac failure, and were not diuretic-resistant. Control patients had no change in therapy. There was sustained improvement in exercise capacity and resting norepinephrine levels lasting for 6 months in six of the eight ultrafiltration treated patients.

CLINICAL EFFECTS: SUMMARY OF PUBLISHED EVIDENCE

Safety

Provided that fluid is not withdrawn too rapidly, none of these trials report unfavourable side-effects.

Efficacy

There is good evidence[3] that fluid can be safely removed by ultrafiltration from heart failure patients including those with diuretic resistance or renal failure. In the presence of diuretic resistance it is clearly the treatment of choice.

Apart from such cases, its role in the treatment of heart failure in general is less clear and it is uncertain whether ultrafiltration is more effective than stepped-up intravenous diuretic in eliminating excess fluid in moderate or severe heart failure. Only three studies bear directly on this question.[10-12]

Costanzo et al.[10] in a multicentre study (total n=200) demonstrated that patients achieved greater short-term weight loss and net fluid loss with 48 hours UF than with increased intravenous diuretics. By contrast, Rogers et al.[11] (in 9 of 18 patients) and Agostoni et al.[12] (in 8 of 16 patients) both found no difference between the two interventions. It should be noted that patients in the latter trials had only moderate, stable, heart failure and that neither of these trials explicitly involved patients with cardio-renal syndrome or diuretic resistance. Thus, apart from its use in diuretic resistant patients or those with cardio-renal syndrome, the short-term clinical benefit of using ultrafiltration rather than diuresis for the management of heart failure is unimpressive. However, there is some evidence of longer lasting benefits.

Duration of efficacy

Three studies have reported that the beneficial effects of ultrafiltration may last for 3 months[10;13] and possibly up to 6 months.[12] Furthermore, according to Agostini et al.[12] these sustained health benefits did not follow when a comparable diuresis was obtained with an intravenous diuretic bolus. Consistent with the reports of sustained benefits, Costanzo et al. reported reduced re-hospitalization in the 90 days following ultrafiltration.[10] Thus, quite apart from its use in diuretic resistant patients,
UF may have sustained beneficial effects when used in heart failure patients.

Costs

Rosenthal et al.[8] indicated a saving of $390 per patient treated by UF compared to intravenous diuretic therapy based on the assumption that UF can save one ICU and one non-ICU day.[8] The RCQT report also supported the possibility (without direct evidence) that UF might be cost-saving based on reduced index hospital stay and a lower readmission rate.[2] By contrast, Bradley et al. estimated that each UF treatment would cost $1,859 more[7] and the NHS's study concluded that treating heart failure by UF would cost £608 more per patient treated.[3]

BUDGET IMPACT AT THE MUHC

The anticipated budget impact of the proposed use of UF at the MUHC will depend not only on the cost items listed in Table 3, but also on factors such as the duration of hospital stay, and the rate and duration of hospital readmissions associated with standard care and UF. These items are listed in Table 4. Clearly, the evidence on which these estimates are based is extremely slender and the derived estimates of budget impact must be considered to be very approximate

However, on the basis of the above estimates, the costs of treatment of heart failure, carried out by standard treatment (in hospital, intravenous, diuretic therapy) or by ultrafiltration can be estimated as shown in Table 3. A sensitivity analysis using Monte Carlo simulation was modeled to take into account the possible variations in input variables listed in Table 4. According to these estimates the costs of treating 50 cases of diuretic resistant heart failure per year are as follows:

- Ultrafiltration- $330,318 (95% CI, $282,196 - $410,635)

Standard Care - $309,644 (95% CI, $262,594 - $400,209)

The proposal to treat 50 patients by UF who would otherwise receive standard care, might result in a budget impact of: $330,318 - $309,644 = $20,674 per year (95% CI= -$76,091. to $107,199.)

DISCUSSION

It is clear from the published evidence that UF, if properly used with an appropriate rate of fluid withdrawal, is a safe and effective method of treating fluid retention in congestive heart failure. In the presence of diuretic resistance it is at least as effective as the conventional approach using increased intravenous diuretics and in most cases is likely to be the treatment of choice. There is suggestive evidence that through its use the length of the index hospitalization for decompensated heart failure may be shortened. The existence and extent of this reduction remains conjectural.

Even less well proven is the possibility that water unloading effected through use of UF may have long-term beneficial effects, lasting three and possibly six months, that are not obtained by use of diuretics. The existence of such an effect needs to be confirmed. If

present, there may well be a case for use of UF in severe heart failure even before the development of diuretic resistance.

Thus, while it is clear that the MUHC should have access to this technology for cases of severely diuretic resistant heart failure, the extent of the use of this technology in cases that have not developed diuretic resistance will depend on possible benefits, as yet unproven. If there is no significant shortening of hospital stay or reduction in readmission rates associated with the use of UF, the cost per patient will be approximately $6,606. However, should such reductions in hospital costs be significant, use of UF may result in net savings. It is clearly most important to obtain this information. It is reported that a North American study is commencing in which some of the relevant endpoints will be followed up, but apparently only for 60 days.[14]

CONCLUSIONS

- **There is sufficient evidence to conclude that ultrafiltration is an effective technology for the management of acutely decompensated heart failure.**

- **UF is the method of choice when patients have become resistant to diuretics or have developed secondary renal failure.**

- **On the basis of several assumptions for which the evidence is insubstantial, it is estimated that the cost of treating 50 diuretic resistant cases by UF instead of standard care, might have a net budget impact of $20,000 per year. [Note however, that this estimate is uncertain. The annual budget impact might be as great as $107,000, or there might be a saving of up to $76,000.]**

- **There is limited evidence that ultrafiltration may have long-term health benefits including improved exercise performance for up to 3, and possibly 6 months, and that these effects are associated with a reduction in re-hospitalization rates. Confirmation of this evidence is urgent.**

RECOMMENDATIONS

- **UF treatment should be available for the management of the estimated 50 diuretic resistant heart failure patients per year in the MUHC. It is recommended that budget be made available for this purpose.**

- **It is recommended that the cardiovascular division undertake a study to identify the extent and duration of health benefits of UF**.

- **Until there is clear evidence of long-term benefit (possibly with an associated reduction in hospital costs), UF should not be used for the treatment of heart failure in the absence of diuretic resistance.**

TABLES

Table 1: Summary of characteristics of relevant studies

Citation;Country ; Follow-up;Funding source	HF type	Treatment	Patient demographics	Comorbidities
Bart, 2005 (RAPID-CHF trial); USA; 3 months; Funded: CHF Solutions Inc.	Acute DHF	UF: Single, 8-hour course of UF with maximum fluid removal rate up to 500ml/hour; diuretics held while on UF; Control: Usual medical care	UF: n=20, median age 67.5 years, 70% male; Control: n=20, median age 69.5 years, 70% male	UF: 35% diabetes, 60% hypertension, 30% prior MI, 45% prior revascularization, 65% Control: 53% diabetes, 65% hypertension, 30% prior MI, 40% prior revascularization,
Costanzo, 2007 (UNLOAD Trial); USA; 3 months; Funded: CHF Solutions Inc.	Acute DHF	UF: 48-hour course with maximum fluid removal rate up to 500ml/hour; Control: IV diuretics at least twice' pre-hospitalization daily oral dose	UF: n=100, mean age 62 (15) years, 70% male; Control: n=100, mean age 63 (14), 68% male	UF: 50% diabetes, 27% COPD, 56% CAD, 74% history of hypertension Control: 49% diabetes, 30% COPD, 48% CAD, 74% history of hypertension
Rogers, 2008 (UNLOAD Trial); USA; 48 hours; Funded: CHF Solutions Inc.	Acute CHF	UF: 48-hour course with maximum fluid removal rate up to 500ml/hour; Control: IV diuretics at least twicce pre-hospitalization daily oral dose	UF: n=9, mean age 64(15), 78% male; Control: n=10, mean age 54(16), 60% male	UF: 78% diabetes, 44% prior revascularization, 44% prior MI, 78%CAD, 78% hypertension Control: 50% diabetes, 40% prior revascularization, 50% prior MI, 60% CAD, 40% hypertension
Agostoni, 1994; Italy; 3 months	Moderate HF	UF: Fluid removal rate 500ml/hr, UF continued until right atrial pressure lowered by 50% of baseline, Usual diuretics continued. Control: IV bolus of furosemide	UF: n=8, mean age 58(1.6) yrs, 87.5% male Control: n=8, mean age 62(2) years, 87.5% male	UF: NR Control: NR
Pepi, 1993; Italy; 3 months	Moderate HF	UF: At a fluid removal rate of 600ml/hour, ultrafiltration continued until right atrial pressure was lowered by 50% of baseline, continued receiving usual dose of diuretics; Control: Patients kept their usual dose of digoxin, furosemide, and captopril	UF: n=12, mean age 57(5) years, 92% male; Control: n=12, mean age 56(5) years, NR	UF: NR Control: NR

Abbreviation: CHF=Congestive heart failure; DHF=Decompensated heart failure CAD= Coronary artery disease IV=Intravenous

Table 2: Adverse events and mortality

Citation ID	UF	Control
Bart, 2005 (RAPID-CHF trial); USA; 3 months	Infection (catheter-related), n=1 Death, n=1 Unrelated to UF, n=1	NR
Costanzo, 2007 (UNLOAD Trial); USA; 3 months	Catheter/needle site, n=3 Filter clotted, n=5 Infection (catheter-related), n=1 Infection (other), n=4 Bleeding, n=1 Hypotension, n=22 Anemia, n=3 Dialysis, n=1 Worsening heart failure, n=39 Myocardial infarction, n=3 Arrhythmias, n=10 Cardiac arrest, n=4 Neurologic, n=5 Death, n=9 (9.6%) Heart failure, n=3 Renal failure, n=1 Unrelated to UF/treatment, n=5	Catheter/needle site, n=0 Filter clotted, N/A Infection (catheter-related), n=0 Infection (other), n=9 Bleeding, n=7 Hypotension, n=10 Anemia, n=0 Dialysis, n=0 Worsening heart failure, n=63 Myocardial infarction, n=2 Arrhythmias, n=7 Cardiac arrest, n=6 Neurologic, n=15 Death, n=11 (11.6%) Heart failure, n=5 Myocardial infarction, n=1 Unrelated to UF/treatment, n=3 Unknown cause, n=2

Table 3: Budget impact

Cost items	Ultrafiltration with Aquadex	Standard care
Annual number of patients treated	50	50
Equipment & personnel cost		
Ultrafiltration apparatus ($27,750) amortized over 5 years/patient	*$111.00*	
72-hour treatment cost (use of 1.5 filter per treatment)	$1,200.00	-
Subtotal per patient	$1,311.00	-
Total equipment & personnel cost [Subtotal x 50]	$65,550.00	-
Hospitalization cost		
Average length of stay (day)*	9	10
CCU cost per day	$560.95	$560.95
Subtotal per patient	$5,048.55	$5,609.50
Total index hospitalization cost [Subtotal x 50]	$252,427.50	$280,475.00
Re-admission cost		
Annual number of patients re-admitted**	11	13
Re-admission LOS (day)**	1.4	3.8
CCU cost per day	$560.95	$560.95
Subtotal per patient	$785.33	$2131.61
Total re-admission cost [Subtotal x 11 or 13]	$8,638.63	$27,710.93
TOTAL TREATMENT COST		
per patient	**$6,606**	**$6,193**
per year (assume 50 patients)	**$330,318**	**$309,644**
95% CI (Monte Carlo analysis)	**$282,196-$410,635**	**$262,594-$400,635**

*Source: RCQT report 2008.
**Source: Costanzo et al., 2005

Table 4: Assumptions used in estimation of budget impact

Items influencing budget impact	Best Estimate	Estimated range
Number of new patients treated/year	50	-
Duration of index hospital stay with Standard care (days, average in Quebec in 2005-06 = 9.7[RQCT]	10	8-12
Duration of index Hospital stay with ultrafiltration (days, estimated reduction from standard care by ultrafiltration = 1 day [RQCT]	9	7-11
Readmissions in first year with Standard care, (average readmission rate, 100 Quebec hospitals, 2003-06 = 26%[RQCT])	13	10-16
Readmissions in first year with ultrafiltration (Costanzo et al., 2007 reported 14% fewer readmissions in the first 90 days post-procedure . 13- 14%of 13 = 1.8)	11	8-14
Days of readmission with Standard care (Costanzo et al., 2007 reported 3.8+/-8.5 days per re-admission)	4	3-10
Days of readmission in first year with ultrafiltration (Costanzo et al., 2007 reported 1.4 +/- 4.2 days per re-admission)	2	1-8

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