Acute Dialysis Quality Initiative 8th Scientific Meeting:
Hepatorenal Syndrome
March 16th-19th, 2010

Acute Dialysis Quality Initiative (ADQI) started in response to concerns about the quality of care delivered to patients with renal disease. The chosen initial ADQI strategy was to follow the path of Evidence Base Medicine by first achieving a critical analysis of the evidence available in the relevant issues. The first goal of such critical analysis was to generate several consensus statements that would describe, classify and interpret the available evidence and define the issues and areas of clinical and laboratory research which require priority attention. The second goal was to achieve dissemination of such consensus statements through publication in the literature. The third goal was to use the focus and impetus provided by such statements to facilitate or conduct issue-orientated research in the field.

The first meeting of ADQI took place in New York (August 2000) and sought to tackle the topic of continuous renal replacement therapy. The meeting was successful and a comprehensive consensus document was generated, which was published. Targets for future research were defined and a large epidemiological study of current practice developed from the deliberations of the meeting. Since then several other meeting have defined important areas of kidney disease management particularly in the field of hospital medicine and acute illness which can be accessed at the ADQI website (www.adqi.net). The ADQI meeting was particularly successful in generating a consensus definition and classification system for acute renal failure (the RIFLE system) which has now been validated in >250,000 patients and has become the accepted acute kidney injury (AKI) definition system in the world. It is with these past achievements in mind that the eighth ADQI meeting on Hepatorenal Syndrome is being convened.

Hepatorenal syndrome (HRS) is a functional and reversible form of renal failure in patients with end-stage liver disease. HRS is defined on the basis of a serum creatinine > 1.5 mg/dL without reference to age, gender or ethnicity. In addition, it’s definition is not reflective of the lower baseline serum creatinine concentrations seen in patients with cirrhosis and at the threshold serum creatinine concentrations currently used to define HRS, significant number of patients do not fulfill the diagnostic criteria. Cirrhotic patients for a given change in GFR tend to have smaller and delayed changes in serum creatinine, resulting in underestimating and impairing the recognition of change in their GFR. As a consequence, a large proportion of patients may lose > 50% of function before the diagnosis of HRS could be considered thus delaying treatment.

HRS confers a dismal prognosis, with median survival time in type 1 disease ranging from one week to one month after diagnosis. There is a critical need for effective treatment options to reverse the acute crisis of HRS in order to prolong survival and improve renal function in those patients awaiting liver transplantation, and also to ameliorate long-term outcomes in patients who are not candidates for transplantation. The base of evidence for widely used existing treatments, both pharmacologic and
nonpharmacologic needs to be clarified. In addition, newer therapies have emerged and a new appraisal of the overall body of data in HRS is warranted. Liver transplant is the only definitive therapy for HRS. In February 2002, the United States adopted the MELD score to rank patients accordingly on transplant waiting lists. One of the variables included in the MELD score is the creatinine. However, the low serum creatinine values that exist in patients with endstage liver disease can affect ranking on transplant waiting lists and thus pitfalls in the allocation system calls for further refinement. With the recent classifications in the diagnosis of AKI and introduction of innovative treatments for HRS, the problems and pitfalls in assessing renal function in cirrhotic patients which delays the diagnosis of HRS in addition to affecting the ranking of patients on the transplant list, here is an increasing need to undertake a consensus meeting to review the current literature on HRS.

The goal of this meeting is to tackle the hepatorenal syndrome and create the basis for its definition and classification, develop an initial understanding of its epidemiology, explore the potential use of biomarkers in its diagnosis, prevention and treatment, review current knowledge in the field of prevention and in the field of treatment and develop the framework for a research agenda in relation to this condition. The process will be based on the efforts of work groups and plenary discussions.

Duties of the participants in this group and pre conference activity will include:
1. Critical review the literature on this topic
2. Identification current knowledge and evidence
3. Classification of current evidence according to evidence based medicine principles
4. Identification of areas of inadequate knowledge
5. Identification of priorities for future research
6. Description of appropriate methodology by which future knowledge should be obtained

**Group 1: Evaluation of renal function in patients with cirrhosis**

a. What are the unique aspects of renal function in patients with cirrhosis
b. How should AKI be defined in patients with cirrhosis
c. Utility of clinical markers in determining AKI in patients with cirrhosis?
d. Utility of equations for estimating GFR in patients with cirrhosis
e. Should creatinine level be used in determination of MELD score?
f. What is the role of novel biomarkers?

**Group 2: Pathophysiology, diagnosis and classification of HRS**

a. Pathophysiology and clinical manifestations of HRS
b. How is HRS defined and classified?
c. How do we distinguish HRS from septic AKI in liver patients?
d. What are the hemodynamic changes in patients with cirrhosis?
e. What creatinine threshold should be used?
f. Should HRS-2 be staged based on CKD stages?
Group 3: Management of HRS
   a. What are the pharmacologic and non-pharmacologic strategies to prevent HRS?
   b. What are pharmacologic strategies to treat HRS?
   c. Do pharmacologic strategies improve patient survival?
   d. Goal directed fluid management in patients with HRS

Group 4: Device Management of HRS
   a. CRRT / Dialysis
      i. Single pass albumin dialysis
      ii. Pretransplant support with CRRT
      iii. Intraoperative renal support during liver transplantation
      iv. Citrate anticoagulation
   b. Liver Assist device
      i. Artificial support
      ii. Bioartifical support

Group 5: Surgical Management of HRS
   a. TIPS
   b. Liver transplantation
      iii. Impact of HRS on liver transplant outcomes
      iv. Liver alone vs combined liver-kidney transplant
      v. Pitfalls in UNOS guidelines for combined liver-kidney transplant
      vi. Kidney after liver transplant

For each group topic studies need to be identified via MEDLINE search, bibliographies of review articles and participants' files. Searches are limited to English language articles. However, articles written in other languages can be used when identified and presented by members of the group. Evidence is classified according to levels per EBM methodology. Qualitative commentary is provided when deemed necessary by the group. However, there is no critical appraisal of individual studies during this phase. Outcomes can be grouped into the major categories: physiologic (eg. blood pressure, BUN, etc.), clinical (short-term morbidity/mortality, long-term morbidity/mortality, renal recovery, functional class/quality of life) and economic. Different types of outcomes are considered separately for each intervention. Animal research is not considered as evidence except that it contributed to commentary. Each work group is composed of three to five members, one who serves as the group facilitator. Summary statements are developed through a series of breakout sessions where individual work group members are required to identify key issues for which guidelines are needed and to classify current state of consensus and identify supporting evidence for each issue. Workgroup members are then required to present their findings to the entire group, revising each statement as needed until a final version is agreed upon. The responsibilities for presenting the findings of the work group to the rest of the participants is shared by each member on a
rotating basis. Group facilitators revise work group findings as needed after each plenary session. Directives for future research are achieved by asking the participants to: a. identify deficiencies in the literature, b. determine if more evidence is necessary, and c. if more evidence is necessary, articulate general research questions. When possible, pertinent study design issues are also considered. Conference activities are divided into three steps: pre-conference, conference and post-conference. In the pre-conference step, the methodology is developed, work groups are assembled and assigned to specific topics. Each group identifies a list of key questions, conducts a systematic literature search and generates a bibliography of key studies. During this stage, the scope of the conference is also defined and some topics are excluded from this phase. During the next step, the conference itself, the methodology is approved by the group and the conference is divided into breakout sessions where work groups address the issues in their assigned topic area, and plenary sessions where their findings are presented, debated and refined. During the first plenary session, the key questions are discussed and debated. Revised versions (some added, some deleted and others rewritten) of each question are then presented at the second plenary. At this point evidence is assembled for each question and summary statements are drafted. These statements are further refined in subsequent plenary sessions until final versions are agreed upon. A writing committee assembles the individual reports from the work groups. Each report is edited to conform to a uniform style and for length. The final reports are posted on the internet (www.adqi.net) and mailed to each participant for comment and revision. Finally, international consultants are identified and reports are sent to them for comment. Once final reports are completed, the writing committee summarizes the individual reports into a final conference document. In detail, the following steps can be summarized to identify the first ADQI conference.

ADQI is a moving process that will produce evidence-based statements on different issues concerning kidney disease. Our effort aims at distilling the evidence and presenting it with perspective and interpretation and at developing a research agenda dedicated to improving patient care in this field. In conclusion, we hope this eighth ADQI meeting will achieve the same level of success and productivity as the first, look forward to lively and sometimes heated exchanges of ideas and count on the expertise of all the members to help continue to move closer to the goal of improving knowledge and practice in the management of acute kidney injury.

**PRE-CONFERENCE ACTIVITY**

Each participant is part of a working group to cover a single topic. Each member is required to perform the tasks listed below. Participants are encouraged to communicate with other group members via email or other means in order to streamline their efforts and work collectively. Participants are also encouraged to communicate with other experts both locally and internationally.

1. **Define a list of questions within the topic**

   For each topic, a list of questions is generated. For example under evaluation of renal function in patient with cirrhosis: What are the unique aspects of renal function in patients with cirrhosis? How should acute kidney injury (AKI) be defined in patients with cirrhosis? What is the utility clinical markers in determining AKI in patients with cirrhosis? What is the utility of equations for estimating GFR in patients with
cirrhosis? Should creatinine level be used in determination of MELD score? What is the role of novel biomarkers?

2. **Perform a systemic literature search**

Participants are required to perform their own literature search to find any additional articles. Search strategy and terms have to be specified and participants have to be prepared to defend any exclusion criteria. In general, the trend is to be as broad and inclusive as possible.

3. **Compile a bibliography**

One complete set of references is brought to the meeting by the group members. A bibliography is compiled prior to the meeting, and this is organized in a single format as used by JAMA (this is only to keep the references in a single format).

4. **Assess the current status of consensus**

It is determined what questions are already fairly settled vs. ones that were not. It is also determined what questions will be likely to be answerable with current literature vs. ones that have insufficient evidence. Each question is rated as either: a. consensus already exists, b. data exist but controversy and/or variability of practice is still present, c. insufficient evidence is available. Note: we do not try to judge the quality of the evidence at this stage.

**CONFERENCE ACTIVITIES: PART 1**

The entire group is asked to consider the methodology for the Acute Dialysis Quality Initiative (ADQI) process. Specific tasks include the following:

1. The incorporation of evidence-based medicine principles into the literature review process. Definition of levels of evidence and terms to be used. Definition of what the literature sources should be and how far back the literature should be reviewed.

2. Determination of what clinical, physiologic, and health economic outcomes should be considered evidence of effectiveness in clinical trials of the treatment of the hepatorenal syndrome.

3. Definition of how, physiologic outcomes (e.g. arterial blood pressure) should be rated in relation to clinical outcomes (e.g. survival, need for long-term dialysis) and health economic outcomes (e.g. total costs, length of hospitalization) in evidentiary tables used for further ADQI consensus statements.

4. Draft and review forms to be used for review of literature and data extraction.

5. Definition of how peer review should be done and who be the peer group.

6. Discussion on how “best clinical practice” will be established in the absence of evidence.

7. Determination of how consensus will be achieved on directions for future research.


**CONFERENCE ACTIVITIES: PART 2**

Breakout sessions are used for each group to catalogue and review the literature in each area and define areas of established consensus as well as areas where consensus is lacking. Each group reviews pre-conference work and presents a draft set of statements that summarize the questions for their topic and
the state of the current literature. The specific tasks for each group were:
Create a list of individuals to serve as consultants (for each topic) for the final consensus
Develop the final list of questions and identify key evidence that should be reviewed. (Each topic requires
a few key references associated with it).

Work groups rate the current status of the literature based on the ratings above (a. b. or c. from above).
A summary statement listing what is needed to proceed further for each question and the current state of
the literature is drafted. The spokesperson presents the draft summary statements and presents findings
from any key studies. Note, at this stage, we do not attempt to develop NEW consensus; that will be
covered in the second stage of the ADQI process. Instead, summary statements listed questions,
describe current practices and note the presence or absence consensus already existing. The entire
group evaluates the statements and suggest revisions. Final statements are drafted "on line" with all
members present. A 2/3 majority vote is required to approve all statements.

POST-CONFERENCE ACTIVITY AND FUTURE PLANS
A writing committee will include the conference directors and 1-2 other members nominated by the group
to compile the findings of the conference. This document will be completed as soon as all the necessary
revisions are made from the original drafts and will be posted on the internet http://www.adqi.net/ for
comment by the remainder of the participants. The period for comment will be limited in time and
revisions will be made accordingly. The final product will be submitted as a manuscript for publication
immediately following this process.

CONCLUSIONS
In conclusion, ADQI is a moving process that will produce evidence - based statements on different
issues concerning kidney disease. Our effort aims at distilling the evidence and presenting it with
perspective and interpretation and at developing a research agenda dedicated to improving patient care
in this field.