SUPPLEMENTAL MATERIAL

Classification of Uremic Toxins and Their Role in Kidney Failure: An Expert Consensus Conference

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This supplementary material has been provided by the authors to give readers additional information about their work.

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Supplemental Methods

The modified Delphi methodology (1) comprises four stages: i) Systematic search for evidence in the available literature; ii) Establishment of clinical and physiological outcomes, as well as measures to be used for comparison of different treatments; iii) Description of current practice and rationale for using current techniques and; iv) Identifying areas where evidence is lacking and therefore research is required. Overall, the consensus process relies on evidence where available, if no evidence is available, expert consensus opinion is relied on.

The consensus conference began with a pre-conference comprehensive literature search and appraisal of scientific evidence to identify key themes that are central to uremia and uremic toxins. Conference participants were divided into three workgroups (Supplemental Table 1) and were tasked with addressing the following themes.: Critical appraisal of limitations in the current definition/classification of uremic retention solutes; Rationale for updating definition and classification of uremic retention solutes and molecules of interest in the field of maintenance hemodialysis and; Proposal of a new classification of solutes of interest in uremia and hemodialysis. Participants were chosen by the conference chair (C.R.) based on their contribution in the field in the last 5 years. In addition, a few individuals were chosen based on experience in managing consensus process. A good representation of the different continents was another criterium and the final selection was based on the availability of the invited experts.

Each workgroup identified relevant studies through the National Institutes of Health PubMed platform, bibliographies of review articles and other files provided by participants. Article searches was generally limited to English language articles. Efforts were made to include mainly evidence from randomized controlled trials, however, other articles were also permissible to incorporate the best available evidence.

One group member served as the group facilitator. The conference chair served as moderator for the virtual sessions. During the sessions, summary/consensus statements were developed, requiring each work group to identify key issues, and classify current state of consensus. The findings of each workgroup were then presented to the entire group in the three plenary sessions for debate, discussion, suggested revisions, where each statement was revised until a final version was agreed upon. After each plenary session, the workgroups revised its findings based on the consensus reached by the whole group. To develop directives for future research, participants were asked to: i) Identify deficiencies in current literature; ii) Determine, where more evidence is necessary and; iii) Articulate research questions for areas, where evidence is lacking. The final product was then assessed and aggregated in a videoconference session attended by all attendees, who approved the consensus recommendations.

After the conference, a writing committee collected and edited the individual conference reports from each workgroup. Those final reports were then summarized by the writing committee into a final conference report, which was mailed to each participant for comment and revision. After approval by each member the final conference document was submitted for publication.

Supplemental Table 1. Information regarding workgroups and work product

Conference Chair	**Group 1**	**Group 2**	**Group 3**
Claudio Ronco (Vicenza, Italy)	*Critical appraisal of limitations in the current definition/classification of uremic retention solutes*	*Rationale for updating definition and classification of uremic retention solutes and molecules of interest in the field of maintenance hemodialysis*	*Proposal of a new classification of solutes of interest in uremia and hemodialysis*
Facilitators	Raymond Vanholder (Gent, Belgium)	Colin Hutchison (Herston, Australia)	Peter J. Blankestijn (Utrecht, The Netherlands)
	Mitchell H. Rosner (Virginia, USA)	Laurent Juillard (Villeurbanne, France)	Mario Cozzolino (Milan, Italy)
	Faeq Husain-Syed (Giessen, Germany)	Li Zuo (Beijing, China)	Ziad Massy (Villejuif, France)
	Hideki Kawanishi (Hiroshima, Japan)	Thiago Reis (Brasília, Brazil)	Kianoush Kashani (Rochester, USA)
	Tammy Lisa Sirich (California, USA)	Manish Kaushik (Singapore, Singapore)	Peter J. Blankestijn (Utrecht, The Netherlands)

Supplemental Table 2. Research recommendations for improving our understanding of uremic solutes, their dialytic removal, and their impact on clinical outcomes

Clinical Outcomes

1. Development of large proteomic/metabolomic databases linked to patient outcomes, quality of life, and uremic symptoms.
2. Identification of a panel of clinical parameters to define adequate dialysis (to replace Kt/V).
3. Determination of the effect of uremic toxin removal strategies on patient-oriented outcomes.
4. Association of uremic toxin levels with outcomes in samples from randomized controlled trials (e.g., HEMO (55)).
5. Studies on outcomes using medium cut-off hemodialysis vs. high-flux hemodialysis (superiority studies) or high-flux hemodialfiltration (non-inferiority studies).
6. Understanding the role of uremic toxins in driving senescence (and surrogate makers of senescence such as epigenetic markers).

Mechanisms of Toxicity

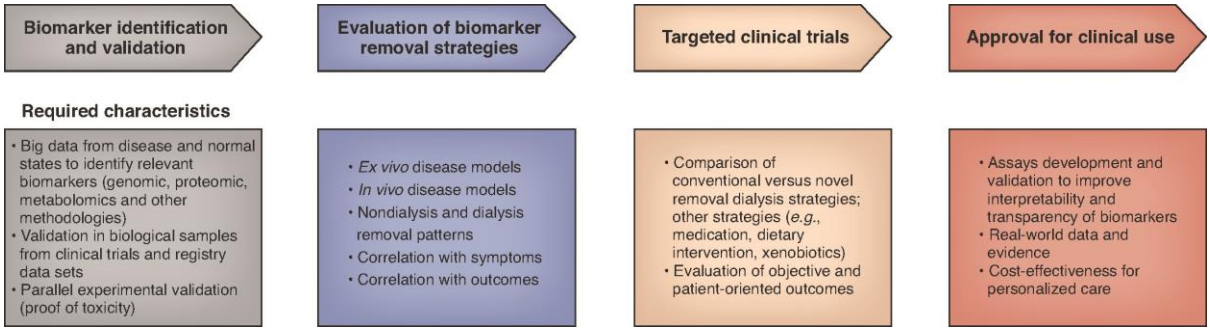
1. Experimental toxicity studies focused on uremic solutes identified in observational studies with hard outcomes (e.g. phenylacetylglutamine).
2. Assessment of the interactions between different uremic toxins.
3. Assessment of the mechanisms of intestinal uremic toxin generation.
4. Development of *in vitro* assays that correlate with "uremic" toxicity.
5. For protein-bound uremic toxins, define whether the free concentration, the protein-bound concentration, or the total concentration determines biological effects.

Development of efficient and sustainable uremic toxin removal

1. Development of novel strategies to increase solute removal or decrease solute concentration.
2. Identification of "marker" uremic solutes that can serve as models for a larger group of toxic solutes (based upon molecular weight, protein binding, and so on).
3. Development of dialysis strategies with evidenced uremic toxin removal that are more compact, more resilient, and more cost-effective.

Supplemental Figure 1. Big data-driven discovery and validation of candidate uremic retention solutes.

Non-omnics and omnics analyses may enable the discovery of novel biomarkers and facilitate a multidimensional understanding of disease biology of uremic toxicity. Subsequent big data methodologies, validation in external cohorts and experimental evidence of toxicity can be simultaneously performed. Uremic retention solutes studied in experimental disease models could be assessed clinically with the use of non-dialysis and dialysis techniques to identify effective strategies for their removal. Biomarkers should then be validated in a larger, diverse group of patients with advanced kidney disease. In the next phase, studies need to assess the impact of biomarker-guided protocols on clinical outcomes. Finally, test platform development with rapid turnaround time, low cost, and high accuracy should be completed before implementation in clinical practice. It should be noted that within the omnics domain, there are still challenges related to the standard of data quality and data quantity needed to capitalize on the full potential of these methods for discovery.



References

1. Kellum JA, Bellomo R, Ronco C: Acute Dialysis Quality Initiative (ADQI): Methodology. *Int J Artif Organs* 31: 90–93, 2008.