Summary

The uremic syndrome was defined by **Vanholder (2003)** as the deterioration of biochemical and physiological functions in parallel with the progression of renal failure.

Uremic illness is due largely to the accumulation of organic waste products, not all identified as yet, that are normally cleared by the kidney. Uremic retention solutes are named "uremic toxins" if they show a biological or biochemical impact that contributes to the uremic syndrome. Their removal, associated with an improvement of quality of life and survival, is the principle aim of extracorporeal renal replacement therapies such as dialysis, and is also the purpose of emerging new therapeutic strategies, such as the application of intestinal sorbents or the pharmaceutical induction of metabolization.

Not all the compounds that accumulate in the end stage renal disease patient are considered as uremic toxins. To define a uremic toxin, it must fulfill certain criteria.

The most recent and acceptable systematic classification of the currently known uremic toxins was generated by the European Uremic Toxin Work Group (EUTox). They classified uremic toxins into:

1) The small water soluble compounds of MW < 500 Da.

2) The larger " middle molecules " of MW > 500 Da.

3) The protein bound compounds.

Contrary to CKD, research on uremic toxins in acute renal failure (AKI) is in its infancy. Some of these alterations of the milieu interne encountered in AKI closely resemble those typically present in CKD but occur at an accelerated rate.

Proteomics analysis represents a new and promising analytical tool whereby all peptides present can be registered and potentially solutes that might be of patho-physiological importance identified, offering the possibility to achieve the unbiased identification of markers or solutes. This approach is facilitated by refinements in analytical techniques together with improvements in informatics.

In general, proteomics can be divided into two broad areas based on the detection methods used:

(1) approaches using mass spectrometry to detect and identify proteins

(2) approaches using arrays or ensembles of binding molecules to detect and identify proteins. The latter approach most commonly utilizes antibodies as the binding molecules.

Despite the wide spectrum of uremic toxins, different classes and different mechanisms, toxicity is not an overall process but it has to be

proven. Only a few compounds have been linked to specific toxic effects on different body systems.

Cardiovascular disease is the main cause of death for patients with chronic kidney disease (CKD).The driving forces for cardiovascular disease in ESRD patients are (i) retention of uremic toxin products; (ii) fluid overload and (iii) inflammation.

The role of uremic solutes in the development of the uremic syndrome has recently been reviewed. The available evidence concerning the most important toxins, which play a potential role in the genesis of vascular disease has been summarized.

Most of these substances are either protein bound, of middle molecular weight or a combination of both, so that their removal with conventional HD is limited.

Infection is still second only to cardiovascular disease as a cause of death in end-stage renal disease (ESRD) patients. Immune system dysregulation in end-stage renal disease patients is a multifactorial process combining profound immunodeficiency with a state of cellular activation. While at the origin of the deficiency, uremic toxins are thought to play a prominent role.

Renal failure causes multiple physiological changes involving CNS dysfunction. In cases of uremia, there is close correlation between plasma levels of uremic toxins [e.g. 3-carboxy-4-methyl-5-propyl-2-furanpropionate (CMPF), hippurate (HA) and indoleacetate (IA)] and the degree of uremic encephalopathy, suggesting that uremic toxins are involved in uremic encephalopathy, also bone metabolism and bone pain.

New therapeutic modalities and future trends have been developed aiming for the best removal of the uremic toxins. For example, development in hemodiafiltration techniques include the on-line mixed hemodiafiltration and reverse mid-dilution to escape from the harmful drawbacks of pre- and postdilution hemodiafiltration. Another methods for clearance of protein-bound uremic toxins include the use of a sorbent into the dialysate and the use of protein leaking membranes.

Removal of middle molecules in HD relies on treatment schedule combining highly permeable membrane (high-flux), enhanced convective clearance and extended treatment duration.

So, many therapeutic modalities that aim to enhance removal of both middle molecules and protein-bound toxins have been developed in the last years. Protein–leaking membranes that provide more clearance of protein-bound toxins now in search of an application. Adding a sorbent to the dialysate is another new different modality.

Various developments in types of hemodiafiltration that overcome its possible complication have been recorded.

These new modalities have demonstrated the evident improvement in clinical outcomes and decreased rates of morbidity and mortality.

It is concluded that both small and middle molecule removal have an impact on survival, so that more than urea removal alone should be pursued.