Uremia. A history of urine in the blood

The term *uremia* was first introduced in 1847; literally translated, it means “urine in the blood.” Today, uremia describes the myriad of symptoms and organ derangements that result from the failure of the kidneys in its normal functions to excrete waste products and to regulate the normal constancy of the body’s internal environment necessary for life. Kidney failure impairs the normal functions of several organs including the brain, heart, stomach, intestines and lungs. Untreated, this can result in permanent organ damage and death.

Uremia typically manifests when the kidney functions approaches 15% or less of normal, though symptoms may be present to varying degree in individuals with less impaired kidney function. This stage of kidney failure is also known as Stage 5 Chronic Kidney Disease (CKD). *Uremic* symptoms include but are not limited to a uriniferous breath smell, metallic taste in the mouth, muscle cramps, changes in mentation, fatigue, itching of the skin, and anemia.

Early stages of kidney disease are typically asymptomatic. Uremia is principally diagnosed by elevation in two laboratory blood measurements: creatinine and urea nitrogen. However, when blood samples from patients with advanced kidney disease are compared to healthy patients, there are over 150 different circulating organic metabolites identified. These so-called *uremic toxins* are likely responsible for some of the cumulative symptoms and derangements in kidney failure.

Because urea nitrogen is principally derived from dietary protein and elevated urea nitrogen is a marker of kidney failure, the prevention and treatment of uremia begins with a reduced protein diet. The role of an altered intestinal microbiome as a contributor to uremia has led to the preparation of oral absorption agents to remove uremic toxins via the gastrointestinal route, but compelling evidence of their success is lacking. Patients with Stage 5 CKD are often prescribed medications such as bicarbonate, vitamin D, and phosphate binders, to combat the associated derangements in kidney failure.

Since the 1960s, the acceptable treatment for uremia has been renal replacement therapy (RRT). The term RRT includes both dialysis and kidney transplantation. What had been theretofore an invariably fatal disease became a treatable one, albeit associated with new complications. Dialysis is a physico-chemical, costly, and invasive treatment that operates as an intermittent therapy prescribed to maximize the removal (*clearance*) of uremic toxins. It does not restore the normal regulatory functions of the kidneys. Dialyzed patients continue to experience uremic symptoms due to inadequate removal of particular metabolites, a toxicity of the dialysis procedure itself and the absence of the normal kidney’s regulatory functions. The persistence of these symptoms is termed the *Residual Syndrome*. Dialysis remains an empiric treatment, with no experimental studies or clinical trials of its long-term effects either in the presence of normal, abnormal or absent kidney function. Kidney transplantation, although not devoid of complications, is the preferred treatment of kidney failure. The new kidney is connected to the recipient’s abdominal blood vessels and urinary bladder so that uremic toxins are naturally removed in the urine, whilst the new kidney assumes the

normal regulatory functions of the kidneys. Following transplantation, the recipient requires lifelong medication (immunosuppression) to enable the foreign organ to evade attack by the host's immune system. Inadequate immunosuppression causes organ rejection, while over-suppression exposes to opportunistic infections.

In the 150 years since the term *uremia* was first coined, it has evolved into a term that more broadly encompasses '*a complex syndrome*' associated with kidney failure. Further research to identify, modify, or remove specific uremic toxins may lead to a more effective therapy of the uremic symptoms of kidney failure.

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