# Charcoal for the management of pruritus and uremic toxins in patients with chronic kidney disease

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**abstract**

*Purpose of the review*: Pruritus is an important, prevalent but often neglected symptom in patients with advanced CKD or on dialysis,. This review addresses the use of activated charcoal and its analogs in the treatment of uremic pruritus, which can be a marker of uremic toxicity.
*Recent findings*: When common causes are corrected and dialysis efficiency is optimized, pruritus is mainly ascribed to the retention of middle and protein-bound molecules, of which indoxyl sulfate and p-Cresyl sulfate are the best studied. While hemodialysis and hemodiafiltration are of limited use, activated charcoal and its analogs offer interesting alternatives. Oral preparations are associated with symptom improvement and a better metabolic pattern, probably via a combination of absorption and modification of the intestinal microbiota. Large studies, in well-phenotyped populations, are needed. Hemoperfusion, commonly used in poisoning pathologies, could be an interesting alternative in hemodialysis patients. The treatment has proved promising in some preliminary and small studies; more research is now needed to test its validity.
*Summary*: Oral activated charcoal and hemoperfusion can be proposed to patients with severe refractory pruritus based on positive, albeit scattered evidence. They also contribute to reducing uremic toxins. Research on their implementation associated with well-established treatments is needed to understand whether they can be used as “uremic detoxifiers”.

**Keywords**: Activated Charcoal, Pruritus, Uremic Toxins, indoxyl sulfate, p-Cresol, Hemoperfusion, CKD, ESRD

**Charcoal for the management of pruritus and uremic toxins in patients with chronic kidney disease**

***Pruritus in CKD-ESKD.***

Pruritus in chronic kidney disease (CKD) patients is a relatively common and troublesome symptom [1-3]. Its prevalence increases as kidney function decreases, suggesting a role for retained toxins and metabolic derangement, but its pathogenesis is still unknown [4]. Abnormalities in phosphate, calcium, magnesium, and PTH balance have been reported as etiologic factors, but their link to uremic pruritus is not always straightforward. They may be at least partly associated with pruritus, given their link with severity of CKD. Similar considerations may hold true for "uremic toxins", a generic term encompassing all retained toxins, but usually employed with specific reference to middle molecules and protein-bound toxins. This is another aspect of CKD that deserves to be studied, given the fact that they are incompletely, and often minimally cleared by hemodialysis or peritoneal dialysis [5-7]. Increased histamine levels, opioid-receptor derangements, and microinflammation have also been suggested as pathogenetic factors; however, data are not fully consistent and heterogeneity in definitions and study populations adds to the confusion [4].
In a large recent study, questionnaires administrated to 3780 patients with non-dialysis CKD were analyzed [8]. This interesting study, one of the largest international cross-sectional studies ever carried out, recalls the importance of this often-neglected problem: the overall prevalence of moderate-to-severe self-reported pruritus was in fact close to 24% in CKD patients. The impact of pruritus on quality of life was high: its severity was associated with the severity of depressive symptoms, and with poor mental and physical health; sleep disturbances were more frequently reported in patients with pruritus, which was more prevalent in Stage-5 CKD and older patients [8]. While we cannot exclude that depression can lead to overrating symptoms, it is possible that depression is at least in part a consequence of severe pruritus, possibly mediated by disturbed sleep. Several factors were associated with a higher prevalence of moderate-to-severe pruritus, notably

chronic lung disease, diabetes, and xerosis, together with higher serum phosphate and lower hemoglobin levels [8]. Once more, establishing a cause and effect relationship could be difficult since hyperphosphatemia and anemia could be expressions of more advanced CKD, or CKD in poor metabolic balance, rather than being the cause of pruritus. The prevalence of pruritus was reported as even higher in end-stage-kidney disease (ESKD), reaching up to 80% of patients with dialysis-dependent CKD, and was found to be more widespread in patients on hemodialysis than in those on peritoneal dialysis [2, 9-11]. According to several experts in the field, awareness of the importance this symptom has in determining the quality of life is typically low, and pruritus is often not only underreported but also inadequately treated [4, 12].

Several therapeutic approaches have been tried, with varying degrees of success. These include topical approaches, with ointments and phototherapy, massage, essential oils or, more recently, Chinese herbal-bath therapy and acupuncture [3, 13-19]. A vast array of systemic treatments has also been essayed, including μ-opioid receptor antagonists and κ-agonists, anti-inflammatory and antihistamine medications, and gabapentin, one of the most widely studied drugs, and, possibly also for this reason, the only one associated with a significant improvement in a recent meta-analysis. Large, well-designed studies on this question are clearly needed [3]

*The "retention hypothesis".*

Uremia is a condition involving metabolic intoxication linked to the retention of molecules of different weights that would normally be physiologically excreted by the kidneys. Most of the signs and symptoms of uremia are explained by this mechanism [5,6]. These molecules, broadly known as uremic toxins, are mostly derived from the catabolism of exogenous proteins; hence, at least part of the variability of symptoms and outcomes in uremic patients can be explained by differences in patients' food habits and metabolic signature [20-22].

Uremic toxins are usually classified on the basis of their molecular weight, water solubility, and protein-binding capacity, factors which influence their removal via dialysis treatment. While low

molecular weight (MW) molecules (MW<500 Daltons) are mostly water-soluble, and thus efficiently cleared by dialysis, middle molecules (MW >500-32000 Daltons) are less efficiently removed by dialysis, especially when they are protein-bound [5,6,23]. Therefore, protein-bound uremic toxins, listed in table 1, are considered more insidious, and less responsive to optimization of dialysis therapy. Very few uremic toxins are routinely dosed, and their variable patterns at least in part explain differences in susceptibility to uremic toxicity [6]. While a number of uremic toxins gained attention in the past, including parathyroid hormone or beta-2 microglobulin, at present the "stars" of uremic toxicity are two protein-bound molecules, indoxyl sulfate and p-Cresyl sulfate [24-27]. Indoxyl sulfate, also known as 3-indoxyl sulfate and 3-indoxyl sulfuric acid, is a metabolite of dietary l-tryptophan, mainly derived from food; conversely, p-Cresyl sulfate is the main representative of a group of solutes for which microbial metabolism substantially contributes to producing toxicity [28,29]. The intestinal microbiota therefore plays a relevant role in this context, and the effect of unbalanced microbiota is more relevant in advanced CKD [30]. Both indoxyl sulfate and p-Cresyl sulfate are small size protein-bound toxins which exert a pleiotropic effect related mainly to interference in the mitochondrial metabolism, oxidative stress, smooth muscle cell proliferation, and endothelial dysfunction [31-35]. Increased levels of these toxins have been associated with cardiorenal syndrome, increased cardiovascular mortality on dialysis, increased mortality in AKI patients, kidney damage progression, coronary and vascular calcification, or cardiovascular and all-cause mortality [34-39].

These observations open new therapeutic frontiers, the possibility of decreasing protein-bound toxins by interventions involving the diet, the intestinal microbiota, or the absorption at the intestinal level of proteins and their potentially toxic metabolites.

*Protein restriction and pre- or probiotic treatment.*

Protein restriction, especially involving animal-derived proteins, can reduce p-Cresol and indoxyl sulfate serum levels in CKD patients. In a study comparing low- with very-low- protein diets,

indoxyl sulfate levels were lower in patients on higher protein restriction, but the data available does not make it possible to directly correlate protein intake with indoxyl sulfate levels; the effect could also at least in part be due to changes in the intestinal microbiota, following dietary modifications (foods richer in fiber and anti-oxidants) [37]. Of note, the ketoacid and amino acid mixture used in Italy is tryptophan free, and this may confer an advantage vis-à-vis places where these preparations contain tryptophan. Unfortunately, no comparative study is so far available.

CKD is an acknowledged cause of dysbiosis, a term indicating a deregulated and potentially harmful unbalance of the intestinal microbiota that is associated with CKD in two ways: the CKD "milieu", uremic toxins, as well as several medications or incorrect dietary management, can alter the ecology of the intestinal microenvironment; on the other hand, alterations in the intestinal flora can shift the metabolic balance towards pro-oxidative and pro-inflammatory conditions, which can further impair the intestinal flora and damage the intestinal barrier, and also represent a risk factor for CKD progression [39].

There is therefore room for probiotics, prebiotics, symbiotics, and bioactive compounds in treating CKD patients, as well as patients with an array of chronic metabolic diseases. Prebiotics such as resistant starch or oligofructose-enriched inulin and probiotics such as bifidobacterium are potentially beneficial interventions, alone or coupled with intestinal sorbents [39,40].

While no study has yet specifically addressed pruritus, and research is relatively recent, evidence of a positive effect of these compounds is accumulating [39,41].

Table 2 summarizes potential means of prevention and therapeutic approaches aimed at reducing the effects of uremic toxins.

***Oral charcoal therapy: activated charcoal.***

Activated charcoal is a powerful, non-selective intestinal adsorbent that is used in various kinds of drug poisoning, mainly in the emergency department [42]. Activated charcoal consists of an amorphous form of carbon polymer deriving from incomplete combustion of carbonaceous organic

matter; it is oxidized (“activated”) by a high-temperature gas flow over its surface: a fine network of pores is formed, dramatically increasing the surface area and its adsorption capacity, which is linked to the number of pores of various sizes [43]. Following oral ingestion, activated charcoal rapidly spreads in the intestine where it is able to non-selectively absorb small molecules as well as several toxic substances [42,44].

The first report on the efficacy of activated oral charcoal in treating dialysis-associated pruritus was a small placebo-controlled, double-blind, cross-over study, involving 11 patients [45]. The study showed that a daily dose of 6 grams for eight weeks significantly decreased pruritus in all but one patient. The effect was independent of variations in phosphate or calcium levels [45]. A few other series were later published: in 1995 Giovannetti et al. described complete or partial remission of severe pruritus in 20 out of 23 hemodialysis patients, treated with a daily oral dose of 6 g of activated powdered charcoal [46]. The beneficial effects persisted for several weeks after discontinuation of oral charcoal.

Oral activated charcoal could be a safe, effective, and low-cost therapy for patients with uremic pruritus but also for hyperphosphatemia, especially when other treatments are not available.

A single-center, randomized controlled study, including 97 patients affected by Stage-3 -4 CKD, demonstrated that administration of a 0.6-1.2 g oral dose of activated charcoal three times a day was effective in reducing serum phosphate levels. A delay in the development of vascular calcifications was also reported [43]

However, non-selective absorption can impede correct bioavailability of several drugs as well as the absorption of some nutrients; interference with the many drugs often prescribed to dialysis patients has not been studied, a problem in common with several widely used, albeit less selective binders [47,48]

***Oral Charcoal Therapy: AST-120.***

Spherical carbon adsorbent AST-120 (Kremezin®) is an odorless black carbon adsorbent consisting of porous particles measuring 0.2-0.4 mm in diameter and is insoluble in water. The substance was approved in Japan in 1991 and is now available in other Asian countries, such as Korea and the Philippines, in doses of 6 g/day in patients with advanced CKD. In spite of the high number of pills that need to be taken (up to 20 300-mg pills per day), it is well-tolerated, and adverse effects were reported in only 5% of patients, most frequently gastrointestinal discomfort, constipation, appetite loss, and nausea [49].

AST-120 has been proposed as a way to remove protein-bound molecules, including indoxyl sulfate, through gastrointestinal sequestration in a dose-response manner [49,50]. In comparative studies, AST-120 adsorption capacity was similar or superior to that of activated charcoal for several uremic toxins. In fact AST-120 seemed to exert a renal protection effect in animal and human studies, thought to be linked to a reduction in indoxyl sulfate [51,52]. Improvement of uremic symptoms, including pruritus, was observed in a multi-center, double-blind placebo-controlled phase-III study performed in non-dialysis Stage-5 CKD patients [53,54]. Pre-registration trials in humans suggest that AST-120 could delay the progression and postpone the start of renal replacement therapy [55-57]. However, two large randomized, placebo-controlled trials (EPPIC-1 and EPPIC-2) found that when AST-120 was added to treatment regimens, this did not have a significant effect on different endpoints, including dialysis initiation, kidney transplantation, and serum creatinine doubling in patients with Stage-4 CKD, despite a shorter estimated median time to primary endpoints for the placebo group (124 vs 170-189 months in the AST-120 groups) [52]. Interestingly, the effect seems to be more pronounced in some patient groups, in particular those with higher comorbidity or a progressive kidney disease; a beneficial effect has in fact been reported in diabetic nephropathy, and a post-hoc analysis of the EPPIC trial suggested a positive effect on patients with relevant proteinuria (> 0.5 g /g of creatinine) [58,59].

Apart from the effects on CKD progression, oral administration of AST-120 appears to have an additive effect in reducing levels of protein-bound uremic toxins in patients on hemodialysis. A cross-over study in 20 dialysis patients showed that oral administration of AST-120 caused a sharp decrease in circulating l indoxyl sulfate (as total and free levels), p-Cresyl sulfate (total and free levels), and phenyl sulfate (free levels ), while indoleacetic acid and hippuric acid remained unchanged [60]. This study, which underlines the need for further research, suggests that AST-120 could be an additional tool for controlling uremia-related complications in patients on conservative management, including low-protein diets (Figure 1 ) [60, 61].

Interestingly, AST-120 was more effective in reducing p-Cresyl sulfate than indoxyl sulfate levels. Since both molecules come from protein fermentation by colonic bacteria, this suggests that AST-120 induces changes in the microbiota, similarly to prebiotics and probiotics, which are generally found to reduce p-Cresyl sulfate more than indoxyl sulfate levels, and that the effect is limited to uremic toxins originating from colonic microbiota [61,62].

Uremic pruritus has not been extensively studied, and the only report specifically addressed to this symptom reports an improvement in patients with generalized pruritus [53].

***Charcoal in extracorporeal techniques for the removal of uremic toxins.***

As previously discussed, pruritus has different etiologies in dialysis patients and therefore responds to different treatments. The most commonly reported forms are those related to a high calcium-phosphate level, with or without high parathyroid hormone levels, which respond to PTH lowering agents, phosphate binders and more frequent dialysis sessions (up to every-day dialysis), in various combinations. Some cases are refractory to these measures, and itching persists in the presence of a high Kt/V, and of a well-controlled calcium-phosphate and PTH balance and can be improved only by kidney transplantation [63]. These are forms that might be due to other toxins, including protein-bound ones.

Protein-bound uremic toxins are in fact poorly removed by conventional dialysis membranes, both in hemodialysis and hemodiafiltration. Super-flux hemodialysis membranes, increasing the dialyzer's mass transfer area coefficient and dialysate flow, protein-leaking dialysis membranes, and coupled plasma filtration adsorption could be ways to improve removal of protein-bound toxins and decrease uremic toxicity [64-68]. However, the clinical application of such treatments is debated, and the loss of important nutrients, first of all albumin, needs to be balanced against higher efficacy in depuration of middle molecules and protein-bound toxins [69-71].

The addition of hemoperfusion on activated charcoal could be an interesting means for reducing the levels of protein-bound toxins, with a favorable effect on symptoms that, as in the case of pruritus, seem to respond at least partially to the removal of protein-bound toxins. There are few studies available on the use of activated charcoal cartridges during hemodialysis and they are often observational studies of patients with refractory symptoms. In the first study that we were able to identify, Morachiello and coworkers treated 12 chronic dialysis patients with coated charcoal (150 g/cartridge) in combination with standard hemodialysis for six months. Patients reported a marked relief from pruritus but concomitantly showed a reduction in PTH (from 552 to 364 pg/ml) and phosphate levels (from 6.9 to 4.6 mg/dl). Relief from pruritus was attributed to PTH absorption [72].

More recently, Li reported a beneficial effect from hemoperfusion in hemodialysis patients with refractory uremic pruritus. Ninety patients treated with conventional hemodialysis (polysulfone membrane low-flux, 1.5 m2) were randomly assigned to receive hemoperfusion every other week, using two different cartridges (HA130-RHA and HA330-RHA) or to a control group [73]. HA130-RHA is widely used in China for intractable itching and refractory hypertension; HA330-RHA removes larger molecules and adsorbs inflammatory mediators and endotoxins, and is employed in the treatment of sepsis, multiple organ failure, acute necrotic pancreatitis, multiple trauma, and crush syndrome [74,75].

In the refractory pruritus study, the cartridge was used together, in series with the hemodialyzer, and removed after 2 hours of treatment, while completing hemodialysis. Compared to controls, hemoperfusion was associated with a reduction in phosphate, PTH, and C-reactive protein levels, as well as with improvements in pruritus scores. The HA330-RHA performed better than HA130-RHA cartridge, thus suggesting that uremic pruritus benefits from the removal of inflammatory mediators and endotoxins, in addition to phosphate and PTH [73]. A medium-term (two-year) study combining thrice-weekly hemodialysis with once-weekly HA130-RHA hemoperfusion showed a decrease in serum leptin, CRP, PTH, IL-6, ß2-microglobulin, and TNF-α, hemoglobin. Furthermore, blood pressure and left ventricular mass index were reduced, and ejection fraction improved. Doses of erythropoiesis-stimulating agents and antihypertensive drugs were reduced. An advantage in survival and quality of life was likewise reported [75,76].

The new generation of low-flux mixed-matrix membranes is far more efficient at removing indoxyl sulfate and p-Cresyl sulfate [77]. The development of mixed-matrix membranes containing incorporated activated carbon is ongoing. In vitro studies suggest that such membranes efficiently adsorbed p-Cresyl sulfate to a level that can even correspond to daily production; they could also be of interest for dialysate depyrogenation [78]. Various challenges still need to be addressed, such as the possibility of particle release into circulation [79]. An in vitro study, not followed by in vivo application, suggested that the addition of a sorbent to the dialysate increased clearances of p-Cresyl sulfate and p-Cresol without changes in urea clearance [80]. With a serendipitous approach, Madero showed that with an intradialytic infusion of ibuprofen, which shares the primary albumin-binding site with p-Cresyl sulfate and indoxyl sulfate, removal of these uremic toxins was increased [81]. These studies, that are still often isolated or small in size, suggest that future studies should be addressed to testing the potential of absorption, balancing lack of selection and the need for treatment of pruritus as well as other signs or symptoms of uremic toxicity in dialysis patients.

***Conclusions***

Pruritus is an important and often neglected symptom in patients with advanced CKD or ESKD, being reported in 25% to over 80% of cases.

When common causes, mainly linked to calcium-phosphate and PTH imbalance are corrected, and when dialysis efficiency is optimized, a relevant number of cases still suffer from this distressing symptom, which is then mainly ascribed to the retention of middle molecules and protein-bound molecules. Among them, indoxyl sulfate and p-Cresyl sulfate are the most studied. Their removal is associated with improved health, slower CKD progression, and decreased pruritus (Figure 2).

While conventional hemodialysis and hemodiafiltration are of limited use in removing these molecules, activated charcoal, used in poisoning to prevent intestinal absorption, offers an interesting alternative. The use of both oral activated charcoal and, more recently, of the spherical carbon adsorbent AST-120, has been associated with decreased pruritus, but large, well-designed studies are needed to verify this as well as other targets. Scattered data on the addition of hemoperfusion to conventional dialysis are promising and need to be repeated on a large scale.

Dialysis membranes with activated carbon are being studied; their interest as “uremic detoxifiers”, beyond the correction of pruritus, underlines the importance of continuous research on dialysis supplies.

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**Key points**:

Oral activated charcoal can reduce indoxyl sulfate, p-Cresyl sulfate and p-Cresol serum levels in CKD and ESRD patients.

Oral activated charcoal can attenuate uremic pruritus; the advantages need to be balanced against the risk of reducing the absorption of life-saving drugs.

AST-120 can have beneficial effects on the progression of CKD and in delaying dialysis start, especially in progressive CKD patients and it is a means of enhancing the efficacy of blood purification in dialysis patients, aiming to prevent uremia-related complications and symptoms, including pruritus.

Although evidence is scattered, and further studies are needed, preliminary findings indicate that hemoperfusion can be used to integrate blood purification in hemodialysis, acting as a “uremic detoxifier”.

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**Table 1. List of the better-known protein-bound uremic toxins**

| **Molecule** | **Mol weight (g/mol)** | **Family** |
|---|---|---|
| 2-methoxyresorcinol | 140 | Phenols |
| 3-deoxyglucosone | 162 | AGE |
| CMPF (3-Carboxy-4-methyl-5-propyl-2-furanpropionate) metabolite | 240 | Furan fatty acid |
| Fructoselysine | 308 | AGE |
| Glyoxal | 58 | AGE |
| Hippuric acid | 179 | Hippurates |
| Homocysteine | 135 | Amino acid homologue |
| Hydroquinone | 110 | Phenols |
| Indole-3-acetic acid | 175 | Indoles |
| **Indoxyl sulfate** | **251** | **Indoles** |
| Kynurenine | 208 | Indoles |
| Kynurenic acid | 189 | Indoles |
| Leptin | 16000 | Peptides |
| Melatonin | 126 | Indoles |
| Methylglyoxal | 72 | AGE |
| $N^{\varepsilon}$-(carboxymethyl) lysine | 204 | AGE |
| **p-Cresol** | **108** | **Phenols** |
| **p-Cresyl sulfate** | **188** | **Phenols** |
| Pentosidine | 342 | AGE |
| Phenol | 94 | Phenols |
| Putrescine | 88 | Polyamines |
| Quinolinic acid | 167 | Indoles |
| Retinol-binding protein | 21200 | Peptides |
| Spermidine | 145 | Polyamines |
| Spermine | 202 | Polyamines |

**Table 2. Potential approaches to reducing the effects of uremic toxins**

***Reducing the generation of toxins***

- Reduce protein intake
- Keep intestinal microbiota healthy (probiotics, prebiotics, symbiotics)
- Uremic toxins decreased by this therapeutic approach: p-Cresol and indoxyl sulfate
- Potential adverse effects: none, if dietary advice is balanced and there is good adherence to nutritional treatment

***Intestinal adsorption of toxins***

- Oral sorbents, charcoal (e.g. AST-120)
- Uremic toxins decreased by this therapeutic approach: small molecules and several toxic substances, including p-Cresol and indoxyl sulfate Potential adverse effects: gastrointestinal discomfort, constipation, appetite loss, and nausea

***Preserve residual renal function***

- maintaining tubular secretion capacity of toxins

***Removal of toxins***

- Peritoneal dialysis
- Hemodialysis (convective transport, protein leaking in HD)
- Combined hemodialysis and hemoperfusion
- Enhanced removal by dialysate sorbents
- Uremic toxins decreased by this therapeutic approach: wide spectrum of uremic toxins (small water-soluble compounds, middle molecules, and some protein-bound compounds) are removed by dialysis and more advanced extracorporeal techniques
- Potential adverse effects: peritoneal and vascular access related complications, hemodynamic imbalance

***Targeting the toxin-induced cell signaling pathway***

- Organic anion transporters (OAT) inhibitors (Probenecid, Cilastatin)
- Antioxidants (reducing oxidative stress)
- Aryl hydrocarbon receptor (AhR) inhibitors
- Nuclear factor-kappa B (NF-κB) inhibitors
- Potential adverse effects: wide range of adverse effects, some of these molecules display significant side effects

Figure 1. Inter-relationship between chronic kidney disease (CKD), cardiovascular disease (CVD) and microbiota-derived uremic toxins. Diets supplying high amount of animal proteins or low

amount of fiber and vegetables create a vicious circle leading to progressive cardiovascular (CVD) and kidney damage (CKD). Hence, diets restricted in animal proteins and rich in plant-origin food are preferable in CKD patients. Favorable effects on gut-microbiota composition and homeostasis are also expected with the use of probiotics, whereas spherical carbon adsorbent AST-120 can reduce circulating levels of p-cresyl sulfate and indoxyl-sulfate.

Figure 2 : A step-wise approach to severe pruritus in patients with advanced CKD or on dialysis