MANAGEMENT OF PRURITUS IN PATIENTS WITH CHRONIC KIDNEY DISEASE

BCRenal
an agency of the Provincial Health Services Authority

Generalized Pruritus

Assessment

General History
- Generalized pruritus
- Duration of pruritus
- Character of pruritus (e.g. paroxysmal vs. continuous)
- Exacerbating and relieving factors
- Detailed drug history
- Treatments tried (prescription/over the counter, topical, oral etc.)

No primary lesions
- Rule out other causes of pruritus with no primary lesions

Primary lesions present
- Consider referral to dermatologist for diagnosis and management

Pruritus with no primary lesions - differential diagnosis:
- Renal pruritus
- Liver disease/cholestatic pruritus
- Hematologic pruritus (Iron deficiency anemia, Polycythemia vera)
- Malignancy (leukemia, Hodgkin and Non-Hodgkin lymphoma)
- Endocrine pruritus (thyroid disease, uncontrolled diabetes)

Other considerations in dialysis patients:
- Ensure dialysis adequacy
- Consider heparin allergy (patient could be switched to NS flush or citrasate dialysate/Na citrate lock solution)
- Consider changing dialyzer, tubing, dialysate (to ultra-pure dialysate fluid), PD solution

Management of Dry Skin — General Measures
1. Bathing recommendations:
   - Fragrance-free sensitive skin bar soap (i.e. Dove sensitive skin® bar soap)
   - Limit use of soap to axillae and groin/perineum
   - Avoid excessive bathing or bathing with hot water
2. Avoid wearing rough clothing, such as wool, over itchy areas.
3. Use mild detergent for clothes/sheets and rinse well.
4. Keep fingernails short and clean. Try not to rub or scratch the itchy areas.
5. Keep your house cool and humid, especially in the winter.
6. Topical emollients:
   - Fragrance-free emollient* BID to TID and especially after bathing; **OR**
   - Baby oil BID to TID; **OR**
   - Menthol 0.25%/camphor 0.25% in emollient* BID to TID
   - For localized pruritus:
     - Consider Capsaicin 0.025% cream, apply sparingly BID-QID (onset of action 2-4 weeks)
     - Pramoxine 1% in emollient BID-TID PRN
7. Consider acupuncture

***Suggested fragrance-free emollients:**
- Cerave® cream
- Cetaphil® cream
- Lipikar® Baume AP & cream
- Aveeno® cream
- Glaxal base® cream
- Cliniderm® soothing cream
- Aquaphor® ointment
- Vaseline® ointment

Consider dermatology referral for Narrowband-UVB phototherapy 2-3x/week

- Oral antihistamine: Hydroxyzine, 10-25mg po QID PRN or Diphenhydramine 25 mg po QID PRN (watch for sedation)
- Gabapentin 100mg po HS, titrate by 100mg Q7days. Maximum dose should be adjusted based on renal function and patient tolerance — see drug monograph. Consider 50mg (compounded capsule) po HS as a starting dose in frail elderly &/or if eGFR < 15mL/min.
- Others:
  - Pregabalin 25 mg PO HS*; titrate by 25 mg Q7days. Maximum dose should be adjusted based on renal function and patient tolerance — see drug monograph.
  - Sertraline, 25 mg po daily, max dose 75mg/d (especially if concomitant depression)
  - If no contraindication, consider doxepin 10mg po hs; titrate by 10 mg Q7days up to 50mg po hs (watch for QT prolongation)
- Go to www.bcrenalagency.ca (Health Professionals > CKD) for information on costs of medications and whether coverage may be available through BCPRA, Pharmacare or Palliative Care benefit plans.

Supplemental Evidence for Treatment Options

In terms of non-pharmacological therapies:

- Moisturizing cream should be considered for all chronic kidney disease (CKD) and dialysis patients as xerosis is prevalent in this population.
- Lotions are not recommended (the higher concentrations of emulsifiers and stabilizers and the lower concentration of lipid in lotions can further worsen dry skin).
- Other non-drug measures, e.g. minimizing the use of soap and hot bath, should also be considered.

The successful use of behavioral therapy or habit reversal techniques has been reported in patients with chronic pruritus; however, their utility in the CKD population has not been studied. We are not recommending steroid based cream or ointment for uremic pruritus, unless the patient has an inflammatory skin condition. Patients with renal pruritus typically have intense pruritus with no primary lesions. If the patient has primary lesions, a dermatology consultation should be considered for diagnosis and appropriate management. A dermatology consult should be considered early for narrow band ultraviolet B (NB-UVB) phototherapy in severe or difficult-to-treat cases. Several locations in British Columbia are available with phototherapy units.

In terms of pharmacotherapies, available literature in CKD non-dialysis patients is limited, with only 4 publications on the topic.[1-4] Most of the pharmacotherapy options suggested in the algorithm have been trialed in hemodialysis (HD) patients. Furthermore, published studies for both populations are of small sample size, from single centres, and have significant drop-out rates or crossover design with a short washout period.

Although there are minimal data confirming the efficacy of sedating antihistamines in the treatment of pruritus in CKD patients, they have historically been used as first-line agents for this indication. Efficacy data regarding non-sedating antihistamines are scarce and contradictory. A negative study comparing loratadine to naltrexone reported loratadine to decrease VAS (visual analogue scale) score in pruritus but this is likely not clinically significant and none of the patients had a decrease in the VAS score > 3 points while receiving this medication.[5] Another study compared desloratadine to gabapentin during a cross-over trial in 22 HD patients. While taking desloratadine 5 mg po 3 times/week, patients' VAS score decrease to a similar extent than while taking gabapentin 300 mg po 3 times/week therapy, with less adverse reactions reported in the desloratadine group.[6] Most experts do not recommend non-sedating antihistamine in alleviating pruritus in CKD patients as they do not cross the blood brain barrier, and therefore may be unable to affect the perception of itch.

Due to the lack of confirmatory studies, the agents listed under limited evidence are not included in the treatment algorithm but could be considered if other typical more cost-effective agents fail.

Positive Studies

Narrow band UVB

A prospective study of 42 HD patients with renal pruritus compared with a matched control group (n=21 in each group) to test the efficacy of NB-UVB was conducted in a hospital in Taipei, Taiwan. The intervention group received NB-UVB 3x/week for 2 weeks and control group was maintained on their prior pruritus treatment. Pruritus intensity was measured with a numerical rating scale at baseline and on alternating days for seven times. The intervention group had significantly lower pruritus intensity than the control group: 3.14 ($p<0.001$) at time seven, 1.71 ($p< 0.001$) at time six and 1.24 at time five ($p< 0.001$).[7]

Another study investigated whether or not NB-UVB phototherapy is an effective treatment for uremic pruritus. A single-blind, randomized (1:1), controlled trial for patients (n=21; 14 HD and 3 PD) with refractory uremic pruritus was conducted where the treatment group received NB-UVB 3x/week for 6 weeks and control group received time-matched exposures to long-wave UVA radiation for 12 weeks. The characteristics of pruritus were assessed at baseline and after 6 weeks of phototherapy. NB-UVB and control groups both had improvement in pruritus intensity. Compared to the control group, the NB-UVB group showed a significant improvement in the involved body surface area affected by pruritus ($p=0.006$) but not in sleep quality. Patients in the NB-UVB group has lower pruritus intensity scores at week 6, 10 and 12 which may indicate a beneficial difference at certain time points but the effect was marginal overall. This study concludes that NB-UVB phototherapy does not show a significant effect in reducing pruritus intensity compared with the control group.[8]

A pilot study of NB-UVB phototherapy was conducted for the treatment of 20 patients (n=20) with uremic pruritus. Ten patients (10 patients left the study) completed the 6-week study period with treatment 3x/week. Eight patients were responders. Of the 10 patients that did not complete the study, 6 were satisfied with the response. In the follow-up period at 6 months post-treatment, 7 responders were assessed and 3 were in remission; however, pruritus recurred in the remaining 4. NB-UVB may be an effective treatment but recurrence of pruritus is a problem.[9]

A meta-analysis of UVB trials for uremic pruritus was conducted using only randomized control trials available on MEDLINE from 1966 to March 1991. Clinically significant outcomes were obtained for 2 of 3 whole-body UVB trials. Meta-analysis of the UVB trials retained the significant effect in analysis of proportions of patients improving under this intervention (pooled odds ratio 18; 95% confidence interval 4 to 161). Trials of lidocaine, charcoal and nicergoline demonstrated either statistically significant improvement in pruritus score or in proportions, but not both. UVB phototherapy was found to be the treatment of choice in moderate to severe uremic pruritus.[10]

Another study evaluated the effect of UV phototherapy on uremic pruritus in 56 patients with chronic kidney disease (52 on HD, 4 PD). Seven patients (n=7) were treated 2x/week for 4 weeks with UVB to ½ of the body and placebo phototherapy (UVA) to the other half. All patients noted generalized improvement without localization of benefit to the UVB side. Patients treated more frequently (3x/weekly) improved faster. Overall, 32 of 38 patients improved after a course of 6 or 8 UVB exposures. Pruritus recurred in 15 patients after a mean remission of 3 months. Sixteen patients remained in remission for 10.6 months after the 1st or 2nd

course of treatment.[11]

Baby oil (topical)

A prospective study of 35 HD patients with pruritus compared with a matched control group (n=35) looked at the efficacy of cool baby oil (10-15°) applied on the affected area for 15-20 minutes 3 times/week prior to HD for 1 month.[12] Baby oil improved VAS pruritus score, the Pittsburgh sleep quality index as well as the SF-36 Quality of life Physical and Mental component scores.

Another prospective study looked at the effect of chilled baby oil (n=30), vs. room temperature baby oil (n=31), vs. routine care (n=32) on the pruritus score of hemodialysis patients.[13] Pruritus improved in both baby oil groups, with no differences were found in the baby oil temperature.

Capsaicin (topical)

In a double-blind, placebo-controlled, crossover trial[14] of 34 HD patients with uremic pruritus, capsaicin 0.03% was compared to placebo x 4 weeks with a 2-week washout. The mean pruritus score (maximum 18 points) was significantly reduced from 15.9 ± 6.3 to 2.5 ± 2.5 in the capsaicin treatment period vs 15 ± 6.0 to 7.2 ± 5.5 in the placebo treatment period.

In another double-blind, placebo-controlled, crossover study[15], capsaicin 0.025% cream was compared to placebo in 17 HD patients with moderate to severe pruritus. Fourteen had marked relief, of whom 5 had complete remission, with prolonged antipruritic effect 8 weeks post capsaicin treatment. No serious adverse reactions were noted.

In an open-label uncontrolled trial and a double-blind, vehicle-controlled trial[16] evaluating capsaicin 0.025% cream in HD patients. Eight of 9 evaluable patients in the open label trial reported marked relief or complete resolution; 12 patients were not evaluable. In the double-blind trial, 2 of 5 evaluable patients reported complete resolution and 2 were not evaluable. No serious adverse reactions were noted.

In a systematic review, six RCTs were assessed in which 3/6 were in HD patients. Due to the poor quality of the HD patient studies, the reviewers were unable to assess the efficacy of capsaicin.[17]

Pramoxine

A double-blind randomized placebo control trial assessed the use of pramoxine 1% lotion in reducing pruritus in HD patients. VAS mean score decreased by 61% in the pramoxine group (n=13) vs. a 12% decrease in the placebo group (n=14). No adverse effects were reported.[18]

Gabapentin and pregabalin

In a retrospective single centre study, gabapentin efficacy and safety was compared between 34 CKD non-dialysis patients and 15 HD patients for restless legs syndrome and/or pruritus.[1] Median gabapentin dosage needed to control pruritus in CKD patients was 100 mg/day. Adverse drug reactions were reported in 47.1% of patients with 17% of patients discontinuing therapy. Conservatively managed CKD patients were found to be at higher risk of experiencing drug adverse effects (47.1% vs. 14.3%).

Another prospective longitudinal study, used gabapentin or pregabalin in 25 CKD patients stage 4 and 5, 40 HD patients and 6 (PD) dialysis patients.[2] Gabapentin relieved itch in 66% (47/71) of patients. 26 patients/71 (37%) of patients had adverse drug reactions (mostly over-sedation) while on gabapentin, with 21 patients stopping the drug. Fifteen of these

patients trialed pregabalin, and 13/16 patients experienced an improvement of their symptoms while on this medication. One patient stopped therapy because of a lack of efficacy and one patient stopped because of side effects.

Another prospective study collected data on the use of pregabalin in 10 HD patients and 2 CKD stage 4 patients with severe intractable pruritus.[3] The average pruritus score prior to treatment was 9.7 ± 0.9 and decrease to 3.7 ± 2.35, 3.2 ± 1.75 and 3 ± 1.5 after 1, 4 and 24 weeks of treatment, respectively ($p < 0.05$). Six patients reported improvement in their symptoms during the first week of treatment. Two patients developed dizziness and somnolence. These patients restarted pregabalin therapy after pruritus relapse a few days after stopping the treatment. Median pregabalin daily dosage was 25 mg (range from 25 mg 3 times/week, 50 mg/day).

A systematic review was recently published reviewing the efficacy of gabapentin in HD patients. Seven studies with a total of 179 patients were included. Most of the patients included had pruritus refractory to antihistamine and topical emollients. Six studies found improvement in pruritus with gabapentin, with a decrease in the VAS score between 5.7 to 9.4 points from baseline by 3 to 8 weeks. Common adverse drug reactions reported were somnolence, dizziness and fatigue with 4/179 patients needing to discontinue treatment.[19]

An open-label series[20] evaluated pregabalin 25mg po HS in 16 HD patients refractory to antihistamine for 2 months (hydroxyzine or desloratadine + levocetirizine). There was a statistically significant difference between the 10-point visual analogue scores before and one month after treatment, 7.44 ± 2.01 vs. 1.7 ± 1.31, respectively. Four patients discontinued treatment due to side effects.

Randomized, cross-over study comparing gabapentin 300mg post-HD and pregabalin 75mg daily in 40 HD patients with a history of neuropathic pain in 6 week treatment blocks. The investigators measured pruritus using a VAS (10cm). There was no statistical difference between these two treatments.[21]

Doxepin

In a randomized, placebo-controlled, crossover trial[22], doxepin 10mg po BID x 1 week was compared to placebo in 24 patients with pruritus resistant to conventional treatment. There was a 1-week washout between treatment periods. Mean age was 48 years. Complete resolution was reported in 58.3% patients with doxepin vs 8.3% with placebo ($p<0.001$) with relative improvement in 29.2% vs 16.7%, respectively. Drowsiness was reported in 50% of patients, which resolved in about 2 days. One patient refused doxepin.

Although there is only one study conducted with doxepin in the treatment of pruritus in HD patients, it has been successfully used in the treatment of intractable pruritus due to its strong anti-H1 histaminic activity. If there is no contraindication to tricyclic antidepressants, doxepin may be tried after other treatments failed.

Sertraline

A retrospective study in 17 conservative CKD Stage 5 patients with pruritus refractory to antihistamine looked at the efficacy of sertraline. Median used daily dosage was 25 mg (range from 25 to 75 mg/day) and the onset of action was 5 weeks.[4]

In another prospective, 19 HD patients with severe chronic pruritus were randomly selected.

Prior to treatment, 9 patients had moderate pruritus and 10 patients had severe pruritus. After taking sertraline 50 mg/day for 4 months, pruritus score decrease to weak in 11 patients while 6 patients had moderate pruritus score and 2 patients had severe pruritus.[23]

Limited Evidence

Activated Charcoal

In an open-label case series[24], 23 HD patients were treated with activated charcoal 6g po daily (30 x 200mg capsules) x 6 weeks. Ten single-blinded patients received placebo treatment prior to charcoal. Ten patients' pruritus completely resolved, ten patients had partial response while 3 were unresponsive. Four patients complained of nausea, weight gain or difficulty with pill burden.

In a double-blind, placebo controlled, crossover study[25], activated charcoal 6g po daily x 8 weeks was shown to relieve pruritus in 10/11 HD patients with idiopathic generalized pruritus (p=0.01). Four patients were non-compliant. No adverse effects were noted.

Although there is some limited evidence suggesting the efficacy of activated charcoal, the product is commercially available as 260mg capsules and may be compounded as 360mg capsules by compounding pharmacies. Therefore, it requires 17 to 23 capsules per day to make up a 6 g daily dose. In addition, activated charcoal may bind to and needs to be spaced apart from other medications during administration. Due to the significant pill burden and potential drug interactions, this option is not listed in the algorithm but may be used as a last resort.

Gamma-linolenic acid (Evening Primrose Oil)

A randomized, double-blind, placebo-controlled, crossover study[26] compared gamma-linolenic acid 2.2% cream vs. placebo for 2 weeks with a 2-week washout in 16 dialysis patients with refractory uremic pruritus. Gamma-linolenic acid cream shows statistically significant change in visual analogue scale and pruritus score compared to placebo.

A randomized trial including 15 dialysis patients compared oral gamma-linoleic acid (2 g/day) or linoleic acid (2 g/day) for 6 weeks.[27] Patients taking gamma-linolenic acid had a significant improvement in their dryness, pruritus and erythema skin symptom scores ($p<0.05$), compared to the patients taking linoleic acid.

Montelukast

In a randomized, single-blind, placebo-controlled, crossover study[28] in 5 HD centers, 16 patients were treated with montelukast 10mg po daily x 20 days vs. placebo with a 14-day washout. Pruritus was reduced by 35% (95% CI, 9.5% to 62.5%) with montelukast vs. 7% (95% CI, 0.5% to 15.9%) with placebo (p=0.002).

Tumeric

In a double-blind randomized control trial conducted on 100 HD patients with pruritus[29], treatment with tumeric 500 mg po 3 times/day for 8 weeks reduced pruritus score greater than placebo: 13.6 ±2.6 vs. 7.2 ± 2.6, p=0.001. No adverse reactions were observed during this trial.

Omega-3 fatty acids

A double-blind, cross-over randomized trial in 4 HD centre looked at the efficacy of Omega-3 1g 3 times/day for 20 days vs. placebo in 22 patients with drug resistant pruritus[30]. Omega-3 group had a pruritus score decreased from 20.3 (95% CI: 16.7-23.8) to 6.4 (95% CI: 2.9-9.8) vs.

17.0 (95% CI: 12.4-21.6) to 14.4 (95% CI: 10.5-18.2) (p=0.0001). No adverse reactions were reported.

Calcipotriol
23 HD patients were enrolled in an open-label study evaluating calcipotriol vs. vehicule solution twice daily for 1 month[31]. Calcipotriol improved the validated modified pruritus assessment score and the VAS pruritus score after 2 and 4 weeks of treatment. Skin dryness was also improved with calcipotriol. No side effects were reported.

Zinc Sulfate
A randomized, double-blind, placebo controlled trial comparing zinc sulfate 440mg po daily in 40 HD patients for 8 weeks. VAS (0-10) was used to assess efficacy and found that both groups had decreased VAS scores after treatment.[32] However, the difference after treatment was higher with zinc sulfate group and statistically significant (3.8 vs. 2.05).

Negative Studies

Naltrexone
A randomized, double-blind, placebo-controlled, crossover study[33] compared naltrexone 50mg po daily x 4 weeks vs. placebo in 23 HD and PD patients with persistent, treatment resistant pruritus. Seven patients did not complete the study. No statistically significant difference was found between the naltrexone and placebo treatment periods.

A randomized, double-blind, placebo-controlled, crossover trial[34] found naltrexone 50mg po daily x 7 days to be effective in 15 HD patients with severe resistant pruritus. The median pruritus scores were reduced from 9.9 (out of 10) to 2.1 for the naltrexone-placebo sequence and 1.0 for the placebo-naltrexone sequence at the end of the naltrexone treatment. Short term efficacy was shown in this study.

Ondansetron/Granisetron
A randomized, double-blind, placebo-controlled study[35] failed to demonstrate ondansetron 8mg po TID x 2 weeks to be more effective than placebo in 24 HD patients.

A prospective, placebo-controlled, double-blind, crossover study[36] compared ondansetron 8mg po TID vs placebo x 2 weeks in 16 HD patients with persistent pruritus. No statistically significant difference in daily pruritus score was reported between both treatment periods.

A randomized, double-blind study compared pregabalin 75mg po twice weekly vs ondansetron 8mg po daily vs. placebo over 12 weeks in 179 patients on dialysis with uremic pruritus. Pregabalin was found to be more effective than placebo and ondansetron (Mean VAS change from baseline = -4.6cm). Ondansetron had a non-statistically significant change from baseline VAS of -0.5cm.[37]

14 HD patients with moderate to severe pruritus were treated with granisetron 1mg po BID for 1 month. Efficacy was evaluated using modified Duo pruritus score at the 1st, 2nd and 4th week. Patients at 4 weeks showed a statistically significant difference in pruritus score.[38]

Tacrolimus 0.1% Ointment
A randomized, double-blind, vehicle-controlled study[39] failed to demonstrate tacrolimus 0.1% ointment (n=12) to be more effective than vehicle (n=8) in relieving uremic pruritus.

Two consecutive treatment periods of 3 weeks segments using 0.1% and 0.03% tacrolimus was conducted in 25 dialysis patients over the course of 6 weeks. Efficacy was assessed by a modified pruritus assessment score and a VAS. Pruritus was reduced by 81.8% after 6 weeks of treatment on the modified pruritus assessment score (median baseline was 11, decreased to median of 2 at week 6; P <0.05). VAS decreased

from median of 7 to median of 4 (P <0.05).[40]

Oral nicotinamide

50 HD patients with refractory uremic pruritus were enrolled in a prospective randomized trial looking at the efficacy of oral nicotinamide vs. placebo.[41] Nicotinamide didn't improve the VAS pruritus score after 4 weeks of therapy in comparison to placebo.

Ergocalciferol

50 HD patients with refractory uremic pruritus were enrolled in a prospective randomized trial looking at the efficacy of ergocalciferol 50,000 units/week vs. placebo for 12 weeks.[42] Ergocalciferol didn't improve the VAS pruritus score in comparison to placebo.

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