International comparisons of prevalence, awareness and treatment of pruritus in people on hemodialysis.

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Abstract

Background and objectives: Uremic pruritus in hemodialysis patients is associated with depression, lower quality of life and mortality. We studied the prevalence, awareness and treatment of pruritus to assess how well this important condition is currently managed internationally.

Design, setting, participants, and measurements: Data from 35,452 hemodialysis patients in up to 17 countries from the Dialysis Outcomes and Practice Patterns Study were analyzed to describe pruritus prevalence from 1996-2015. Data from 6256 patients and 268 medical directors in 17 countries in 2012-2015 were analyzed to describe predictors, effects, medical directors’ awareness and treatment of pruritus.

Results: Patients very much or extremely bothered by itching declined from 28% in 1996 to 18% in 2015. In 2012-2015, among patients nearly always or always bothered by itching: pruritus had a major effect on work and social life; 18% used no treatment for pruritus; 17% did not report itching to healthcare staff. 69% of medical directors underestimated the prevalence of pruritus in their unit. Managing high serum phosphorus and low Kt/V were ranked as the most important interventions but no relationship was found between these factors and pruritus. 57% of medical directors used oral antihistamines for first-line chronic treatment of pruritus. Gabapentin was used by 45% as first, second or third line treatment. Nalfurafine was only used in Japan.

Conclusions: The prevalence of pruritus in people on hemodialysis is decreasing but remains underestimated. Large numbers of hemodialysis patients with severe pruritus do not receive treatment. There is wide variation in the use of unlicensed medications for the treatment of pruritus. These data provide a benchmark for initiatives to improve the management of uremic pruritus.

Key words: Uremic pruritus, gabapentin, pregabalin, nalfurafine, quality improvement, DOPPS
**Introduction**

Uremic pruritus is common in people with chronic kidney disease [1] including in those on maintenance hemodialysis (HD) [2]. It is associated with substantially reduced quality of life, depression, poor sleep quality, and increased mortality [2] (Supplementary video 1) but has been under-recognized by healthcare providers [3,4, 5]. Research into pruritus is a high priority for patients [6].

Treatment of pruritus can be graded according to the severity of symptoms. Patients with mild or localized symptoms may prefer topical treatment whereas more severe or generalized itching may require systemic treatment [7]. Four randomized controlled trials of a total of 138 patients with severe pruritus have shown gabapentin to reduce itch by between 4.6 and 6.4 cm more than placebo on a 10 cm visual analogue scale [8, 9] (Supplementary video 2). Pregabalin (n=67) reduced itch severity by 4.6 cm more than placebo (n= 57) and also improved sleep quality and health-related quality of life [10]. In a case series of 71 patients with severe pruritus, 85% were relieved of itching with gabapentin or pregabalin [11]. Use of these agents is supported by European dermatology guidelines [7] and a Cochrane systematic review [12].

Nalfurafine, a kappa-opioid receptor agonist, reduced the severity of itch by 0.95 cm more than placebo on a 10cm visual analogue scale score in one randomized controlled trial [13] and by 0.9 cm and 1.0 cm more than placebo in a second using two doses [14]. Single randomized controlled trials of turmeric, montelukast and zinc sulfate have shown a significant reduction in itch compared with placebo and warrant further study [15-17].

We have conducted a pruritus-related survey in 17 countries in the Dialysis Outcomes and Practice Patterns Study (DOPPS) to assess how pruritus is currently managed and provide a benchmark for quality improvement initiatives.
Materials and Methods

Patients and Data Collection

The DOPPS is an international prospective cohort study of HD patients ≥ 18 years of age. Study patients are enrolled randomly from a representative sample of randomly selected HD facilities within each nation at the start of each study phase, as described previously [18,19]. Study approval was obtained by a central institutional review board. Additional study approval and patient consent were obtained as required by national and local ethics committee regulations.

To study changes in pruritus prevalence over time we analyzed data from 51,062 HD patients enrolled in the DOPPS at the beginning of DOPPS phases 1-5, i.e. 1996-2015, from up to 21 countries (Figure 1). All patients were offered a questionnaire about their health, care, quality of life, and symptoms. 39,553 returned their questionnaires and of those 35,452 answered the question regarding how bothered they were by itchy skin.

To study current awareness and treatment of pruritus, we studied 8621 patients enrolled at the start of DOPPS 5, i.e. 2012-2015. 6256 (73%) indicated how much they were bothered by itchy skin.

During the second year of DOPPS 5, i.e. 2013, additional questions were asked of patients in 17 countries (excluding Australia, China, France, and New Zealand) about the impact of itchy skin. Of 5884 patients who returned their questionnaires, 5436 patients indicated whether they were bothered by itchy skin, and 4219 patients (in 278 facilities) responded to at least one of the eight additional questions. 268 medical directors of 337 participating study sites in these 17 countries completed a survey about their treatment practices for patients with pruritus. The majority of non-responders (41 of 69) were in the US.

Demographic data, comorbid conditions, laboratory values, and medications were abstracted from patient records. In DOPPS 5, medication lists were ascertained at study entry and updated during study follow up. Patient self-
reported health measures were collected through questionnaires provided at enrolment and annually thereafter.

**Definitions**

In each DOPPS phase from 1996-2015, patients indicated how much they were bothered by itchy skin by responding to the question: “During the past four weeks, to what extent were you bothered by: itchy skin?” Response options were: 1) Not at all bothered, 2) Somewhat bothered, 3) Moderately bothered, 4) Very much bothered, and 5) Extremely bothered. In the 2nd year of DOPPS phase 5 (2013-2014), a section about the impact of itch on patients’ lives was added to the survey, including questions on feelings of depression and embarrassment, and the effect on work and social interactions, from the Skindex-10 [20]. All questions in this section were worded as follows: “During the past week, how often have you been bothered by …”, with responses ranging from 0 (never) to 6 (always) on a 7-point Likert scale. Scores of 5 or 6 were interpreted as being ‘nearly always or always’ bothered.

In 2013, medical directors were asked to estimate the prevalence of pruritus among their patients and describe their typical treatment practices. Questions asked whether the following medications were for first, second, or third line chronic use therapy, acute use, or never prescribed for pruritus: IV corticosteroids, gabapentin, antidepressants, anti-anxiolytics/sedatives, or opioids for patients who are not referred to a specialist. Patient medications were checked for prescriptions of gabapentin, pregabalin or nalfurafine during the entire DOPPS 5 study period (2012-2015). The timing of prescription was not linked to the timing of the patient survey.

**Data Analyses**

Associations of patient characteristics presented in Supplementary Table 1 were tested in adjusted multivariate logistic regression with odds of being at least moderately bothered by itching. Models were adjusted for age, sex, dialysis vintage, 13 summary comorbidity measures (coronary artery disease, cancer, other cardiovascular disease, cerebrovascular disease, congestive heart failure,
Results

Prevalence and severity of pruritus

The percentage of patients very much or extremely bothered by itchy skin declined between 1996 and 2015 from 28% to 18% (Figure 1). Similar results were seen in countries participating in all five DOPPS phases (data not shown).

In DOPPS 5 (2012-2015) the percentage of patients at least moderately bothered by itchy skin ranged from 26% in Germany to 48% in the United Kingdom (UK); 13% (Germany) to 26% (UK) were very much or extremely bothered (Figure 2).

In the DOPPS 5 cross-sectional sample, mean values or prevalence of nearly all patient characteristics were similar across the categories of pruritus severity (Table 1). Patients not responding to the questionnaire differed slightly in age and ferritin.

Patients at least moderately bothered by itchy skin were slightly older and had a higher median C-reactive protein. Multivariable logistic regression analyses confirmed associations of older age and higher C-reactive protein with worse pruritus (Supplementary Table 1). Serum albumin was negatively associated with pruritus severity and patients with hepatitis B or C were more likely to be bothered, as found previously [2]. However, no association was observed with serum phosphorus, calcium, calcium-phosphorus product, parathyroid hormone (PTH), Kt/V, and hemodiafiltration.

Symptom burden due to pruritus
Patients very much or extremely bothered by itchy skin were also bothered by dry skin (84%) and 60% frequently had restless sleep (Table 1). Patients who were nearly always or always bothered by itching in the past week were much more often: 1) bothered by the appearance of their skin, 2) frustrated, annoyed and depressed by their itching, 3) bothered by the effects of itching on interactions, or the desire to interact, with others, and 4) bothered by itching so as to make it hard to work (Table 2).

Approximately one-third of patients bothered by itchy skin were most bothered by itching at night, and nearly 50% were bothered either at all times throughout the day or not at any specific time (Supplementary Table 2). There was no relation of itching with the timing of the dialysis treatment for most patients (61%), whereas 15% indicated itching was worst during the dialysis session, 9% soon after a session, and 14% on non-dialysis days.

**Nephrologists’ awareness of pruritus**

Overall, 65% of medical directors estimated that <5% of their patients suffered from severe pruritus. Medical directors underestimated the prevalence of pruritus in 69% of facilities. In the large fraction of facilities where 21-50% of patients reported having severe pruritus, only 1% estimated the same prevalence of pruritus in their facility. Facilities with the lowest prevalence of patient-reported itching tended to have a higher medical director estimate of the prevalence of severe pruritus (Supplementary Figure 1).

Overall, patients bothered by itchy skin were most likely to report symptoms of itching to a nephrologist (42%), followed by a nurse or other dialysis staff member (32%), a dermatologist (18%) or a primary care doctor (16%; categories not exclusive). However, 17% of patients nearly always or always bothered by itchy skin had not reported their symptoms to any healthcare provider. This varied from 8% in Italy and 12% in the Gulf Cooperation Council countries to 21% in Sweden and 33% in the US (see Supplementary Table 3).

**Treatment of uremic pruritus**
Health care providers treating pruritus

In Germany, pruritus treatment was largely determined by nephrologists, the majority of medical directors referring <5% of patients (Figure 3). In the US, Sweden, and Italy, approximately 30% of medical directors referred >20% of patients with pruritus to a dermatologist, compared to 11-14% of medical directors in Spain and Russia.

Overall, a little over half of patients reported that treatments were most often prescribed by a nephrologist; prescription by other healthcare providers ranged from 19% by a primary care doctor to 24% by a dermatologist; percentages were similar for patients who were nearly always or always bothered by itchy skin. (Supplementary Table 4)

Therapeutic options for severe pruritus

Medical directors ranked five therapeutic options for patients with severe pruritus in order of importance (Supplementary Table 5). Phosphorus control in patients with high serum phosphorus was ranked as most important in every DOPPS country and overall by 60% of medical directors. Increasing dialysis dose in patients with low Kt/V, increasing prescribed treatment time in patients with short treatment time, and lowering PTH levels in patients with high PTH were ranked second to fourth. Use of prescription medications for pruritus was ranked as least important by 45% of medical directors.

Use of medication for pruritus

Sixty-eight percent of patients nearly always or always bothered by itchy skin reported using topical treatments, 28% used oral medications, and 18% reported taking no treatment to relieve their itching. The latter varied from 8% in Japan and 9% in the Gulf Cooperation Council countries to 29% in the US, and 45% in Russia (Supplementary Table 6). UV light therapy was rarely used.

In patients with pruritus not referred to a skin specialist, antihistamines were most commonly used in all countries (Supplementary Table 7). Overall, 57% of medical directors used oral antihistamines (prescription or over the counter)
23% topical antihistamines as first-line chronic treatment of pruritus. 9% reported using topical corticosteroids as first-line treatment.

Gabapentin was used as first-line treatment in some facilities in the Gulf Cooperation Council countries, the US, UK, and Germany (Supplementary Figure 2). All nephrologists in Germany and a majority in the UK and Turkey reported using gabapentin for chronic itching either as first, second, or third line therapy. In all other countries, the majority of nephrologists never used gabapentin, ranging from 100% in Japan and Russia to 55% in the US.

Patient-level data indicated that among all patients bothered by itching, 7% were prescribed gabapentin, 4% pregabalin, 5% nalfurafine, and 85% none of these agents during DOPPS 5 follow-up. Overall, gabapentin prescription, for any indication, varied from 0% in Japan and Russia to 21% in the US during DOPPS 5 follow-up. Pregabalin was only prescribed, for any indication, in the UK, Germany, Canada, and Spain. Nalfurafine was only used in Japan, where 15% of patients bothered by itchy skin were prescribed nalfurafine.
Discussion

Pruritus continues to be common among people on HD, although there has been a decline in prevalence of severe pruritus over the last 20 years. While mild pruritus may be a nuisance, severe pruritus has a major negative effect on patients’ lives. They are often bothered by the dryness and appearance of their skin and are frustrated, annoyed, and depressed by their itching, which has major impact on their social and working lives. The majority also suffers restless sleep, which is associated with depression and increased mortality [2].

Nephrologists in all DOPPS countries under-estimated the prevalence of itching in their patients. Whilst reporting bias may have affected medical directors’ estimates, these findings extend previous reports [3, 4, 5]. Medical directors may have interpreted the prevalence of pruritus to refer either to the percentage of patients with a diagnosis of pruritus or with currently severe itching, the latter being a lower figure if pruritus is treated effectively. Facilities with the lowest prevalence of patient-reported itching tended to have a higher medical director estimate of the prevalence of severe pruritus, suggesting that those more aware of pruritus were more likely to give effective treatment.

Many patients did not report symptoms of itching to clinicians. Even among those who were nearly always or always bothered by itchy skin, 17% had not reported their symptoms to any healthcare provider. Studies in renal [4] and non-renal populations [21] suggest that reporting of itch may rely on patients’ resilience to symptoms, language ability, available time, opportunity during the consultation, and whether they expect health professionals to accept itch as a problem. This emphasizes the need for the renal team to inquire routinely about itching rather than to wait for patients to volunteer this symptom. Systematic use of tools that collect subjective and objective patient-generated data on pruritus [22] may prompt and inform discussions about itch and support treatment decisions.

Wide variation between countries was found in the percentage of patients with pruritus referred to a skin specialist. In a recent German study, 19% of HD
patients with chronic itch primarily had diseased skin and such patients may benefit from a specialist evaluation [23].

The treatment ranked most important by a large majority of nephrologists was dietary counselling and/or a change in the phosphate binder regimen. This suggests most nephrologists believe that high serum phosphorus is a major cause of pruritus. In earlier DOPPS data, Pisoni et al. showed strong associations between the likelihood of being moderately, very much or extremely bothered by itchy skin and having a serum phosphorus $\geq 5.5$ mg/dl (1.8 mmol/L) or an increased calcium-phosphorus product [2]. However, large differences in the odds of patients having pruritus remained after extensive covariate adjustment, indicating that serum phosphorus and calcium/phosphorus product did not explain a large proportion of pruritus.

Furthermore, an association between these measures and pruritus is no longer observed in the 2012-2015 data, a finding supported by other recent studies [11, 20, 24]. There is no published interventional study showing that lowering serum phosphorus improves pruritus. Emphasizing restriction of phosphate intake in patients with pruritus may lead to inadequate nutrition and inappropriately burden patients with responsibility for their own symptoms; see Supplementary video 1.

The intervention ranked next most important was increasing dialysis dose (Kt/V). In a study from 1995, increasing Kt/V from a mean of 1.05 to 1.24 led to an improvement in pruritus [25]. However, no association between Kt/V and pruritus was found in the current study where the mean Kt/V was 1.5, consistent with other recent studies [2, 24].

Many nephrologists would change the vitamin D or cinacalcet regimen to lower an elevated serum PTH in patients with severe pruritus. The link between hyperparathyroidism and pruritus originates from early reports of improvement in itching after parathyroidectomy [26, 27]. However, many patients with severe
Pruritus do not have elevated PTH levels [11] and no association has been shown between pruritus and PTH in this and other studies [2, 20, 24].

The finding that patients with more severe pruritus have lower serum albumin suggests an association between pruritus and malnutrition-inflammation complex syndrome. An association between pruritus and C-reactive protein was reported in two studies [28, 29] as in the present study. A further study demonstrated an association between pruritus and interleukin-2 but not with C-reactive protein or other cytokines [30].

Use of prescription medications was ranked lowest out of the five treatment interventions. Topical treatments were the most commonly used medication and may be preferred by patients bothered by dry skin. Most nephrologists in all countries use antihistamines as first line drug treatment. Treatment with the antihistamine ketotifen has been shown to reduce pruritus compared to conventional therapy [31] but in a comparative trial without a placebo arm, ketotifen was less effective than gabapentin [32]. Another uncontrolled trial of ketotifen showed no effect on pruritus and uncontrolled trials of hydroxyzine and chlorphenamine showed a partial or no effect [32]. Plasma histamine levels are not associated with the severity of pruritus [33] and patients frequently report that antihistamines are ineffective [11, 21, 34]. It has been suggested that antihistamines should be tried first because they are unlikely to be harmful. However, the side effects of drowsiness and dizziness were found to be the same with ketotifen and hydroxyzine as with gabapentin [28]. The lack of a consistent effect of antihistamines is consistent with the findings of functional MRI brain imaging studies in HD patients with pruritus that show normal responses evoked by histamine itch but abnormal responses evoked by cowhage itch [35].

Gabapentin and pregabalin have effects on pruritus, insomnia, and restless legs syndrome, possibly mediated by reducing the excessive resting brain activation shown on functional MRI scans [35]. Their use for pruritus is unlicensed and varies widely between countries. Nalfurafine, an oral κ-opioid receptor agonist, is currently only approved for use in Japan. It may have a direct effect on the
brain and/or provide positive feedback from the skin at the level of the spinal cord. Its effect on itching in randomized trials was less than gabapentin and its commonest side effect is insomnia [14]. There remains a need for a more robust evidence base for these and other agents such as turmeric, montelukast, zinc sulfate, and nalbuphine [15-17, 36].

The current model of clinical practice is failing to identify and treat many patients severely affected by itching. There is a major opportunity to improve the health and wellbeing of chronic kidney disease patients through increased awareness of pruritus and the greater use of effective treatments. This could be achieved by systematic efforts to: 1) develop and implement treatment guidelines; 2) include pruritus monitoring and treatment in performance management schemes [35]; and 3) routinely collect itch prevalence and severity data in registries.

This study has a number of limitations. The patient response rate was 73%. The medical director response rate was 80%, with 59% of no-responders being in the US. The prevalence of itch may be affected by reporting bias; patients who are bothered by itchy skin may be more or less likely to respond to the survey. Similarly, medical directors unaware of the true prevalence of pruritus may be more or less likely to respond. Cross-sectional associations between pruritus and patient characteristics do not imply causation and we did not study the effect of characteristics over time on the development of pruritus.

In summary:
Although there has been a reduction in the proportion of hemodialysis patients affected by itching over the last 20 years, in 2012-2015 nearly one in five hemodialysis patients were very much or extremely bothered by itching. Nephrologists substantially underestimate the number of patients affected by itching. Of patients who were nearly always or always bothered by itching, 17% did not report their symptoms to a healthcare professional and 18% were not receiving treatment for their itching. Medical directors ranked phosphorus control and increasing Kt/V as the most important therapeutic options for patients with severe pruritus but neither phosphorus nor Kt/V were associated
with itching. There is wide variation in the use of gabapentin and pregabalin for the treatment of pruritus. There is a major opportunity to improve the health and wellbeing of hemodialysis patients through increased awareness of pruritus and the greater use of effective treatments.
Disclosures

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References


### Table 1: Patient characteristics according to the extent to which patients were bothered by itchy skin. Data from patients enrolled at the start of DOPPS phase 5, i.e. 2012-2015.

<table>
<thead>
<tr>
<th>To what extent were you bothered by itchy skin during the past 4 weeks?</th>
<th>No response*</th>
<th>Not at all</th>
<th>Somewhat</th>
<th>Moderately</th>
<th>Very much</th>
<th>Extremely</th>
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<tr>
<td>Total sample, N</td>
<td>2365</td>
<td>2111</td>
<td>1840</td>
<td>1188</td>
<td>692</td>
<td>425</td>
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<tr>
<td>Total sample, %</td>
<td>27</td>
<td>20</td>
<td>17</td>
<td>11</td>
<td>6</td>
<td>4</td>
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**Patient characteristics:**

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<th>60</th>
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<td>Age, years</td>
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<td>62(15)</td>
<td>62(15)</td>
<td>63(15)</td>
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<tr>
<td>Time on dialysis, years</td>
<td>5.1(5.6)</td>
<td>5.4(6.2)</td>
<td>5.8(6.2)</td>
<td>5.3(5.7)</td>
<td>4.9(5.4)</td>
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<td>BMI, kg/m2</td>
<td>26(6)</td>
<td>26(6)</td>
<td>25(6)</td>
<td>26(7)</td>
<td>26(6)</td>
<td>26(7)</td>
</tr>
<tr>
<td>Treatment time (min)</td>
<td>231(37)</td>
<td>237(34)</td>
<td>237(35)</td>
<td>235(32)</td>
<td>232(32)</td>
<td>232(29)</td>
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<tr>
<td>Hemodiafiltration</td>
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<td>20%</td>
<td>16%</td>
<td>17%</td>
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<td>Smoker</td>
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<td>21</td>
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<td>6</td>
<td>8</td>
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<td>Labs:</td>
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<tr>
<td>Hemoglobin, g/dL</td>
<td>10.9(1.4)</td>
<td>11.0(1.4)</td>
<td>11.0(1.4)</td>
<td>11.0(1.4)</td>
<td>11.0(1.4)</td>
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<tr>
<td><strong>Parathyroid hormone, pg/mL</strong></td>
<td>355(379)</td>
<td>355(416)</td>
<td>348(449)</td>
<td>346(496)</td>
<td>322(345)</td>
<td>349(430)</td>
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<tr>
<td><strong>White Blood Cell count</strong></td>
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<td>6.7(2.1)</td>
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<td>6.7(2.2)</td>
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<td><strong>Albumin (g/dL)</strong></td>
<td>3.7(0.5)</td>
<td>3.8(0.5)</td>
<td>3.7(0.5)</td>
<td>3.7(0.5)</td>
<td>3.7(0.5)</td>
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<td><strong>Calcium (mg/dL)</strong></td>
<td>8.9(0.8)</td>
<td>8.9(0.8)</td>
<td>8.9(0.8)</td>
<td>8.9(0.8)</td>
<td>8.9(0.8)</td>
<td>8.9(0.8)</td>
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<tr>
<td><strong>Phosphorus (mg/dL)</strong></td>
<td>4.9[4.0,5.9]</td>
<td>4.9[4.1,5.9]</td>
<td>5.1[4.2,6.0]</td>
<td>5.0[4.0,5.9]</td>
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<td>5.0[4.1,6.1]</td>
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<tr>
<td><strong>Single Pool Kt/V</strong></td>
<td>1.5(0.3)</td>
<td>1.5(0.3)</td>
<td>1.5(0.3)</td>
<td>1.5(0.3)</td>
<td>1.5(0.3)</td>
<td>1.5(0.3)</td>
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<tr>
<td><strong>CRP (mg/L)</strong></td>
<td>4.7[1.5,13.2]</td>
<td>3.0[1.0,8.0]</td>
<td>2.7[1.0,7.0]</td>
<td>4.0[1.0,9.7]</td>
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**Patient reported measures:**

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<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bothered by dry skin</strong></td>
<td>14%</td>
<td>21%</td>
<td>68%</td>
<td>81%</td>
<td>87%</td>
<td></td>
</tr>
<tr>
<td><strong>Have restless sleep</strong></td>
<td>29%</td>
<td>36%</td>
<td>46%</td>
<td>57%</td>
<td>66%</td>
<td></td>
</tr>
</tbody>
</table>

Footnote: Data shown as mean (standard deviation), median [interquartile range], or column percent.
Non-response rate was 27% overall, varying from 9% in Turkey to 46% in Canada.

A. Hemodiafiltration (HDF) excludes US and Canada due to lack of use; \( N=6024 \)

B. Smoker defined as someone indicating being a current smoker or stopped smoking within past year; measure missing for all patients from US Large Dialysis Organizations; \( N=5871 \)

C. CRP is restricted to facilities that reported measurement in at least 50% of patients (excludes US), \( N=2607 \)

D. Measure shows % patients that selected moderately, very much, extremely bothered (vs not at all, somewhat) in response to the question on the Patient Questionnaire: “During the past 4 weeks, to what extent were you bothered by each of the following: Dry Skin?” \( N=6152 \); missing for most ‘No response’ patients since they did not return the questionnaire

E. Measure shows % patients that selected: “3=Occasionally or a moderate amount of the time (3-4 days)” or “4=Most or all of the time (5-7 days)” vs “1=Rarely or none of the time (less than 1 day)” or “2=Some or little of the time (1-2 days)” in response to the question on the Patient Questionnaire: “During the past 4 weeks, my sleep was restless” \( N=6025 \); missing for most ‘No response’ patients since they did not return the questionnaire
Table 2: Effects of pruritus on daily living in patients who were nearly always or always bothered by itchy skin. Data from the second year of DOPPS 5, i.e. 2013, in 17 countries.

Footnote: Table shows percent responses to questions among patients who said ‘Yes’ to ‘Are you bothered at all by itchy skin?’ and selected 5 or 6 (‘Nearly Always or Always bothered’) on 0-6 scale in response to ‘During the past week, how often have you been bothered by: your itching?’ N=1023; number of responders to each question was within 6%.

<table>
<thead>
<tr>
<th>Among patients nearly always bothered by itchy skin during the past week, frequency of being bothered by:</th>
<th>0 (Never)</th>
<th>1 to 3</th>
<th>4 to 6 (Always)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Being annoyed about your itching</td>
<td>3</td>
<td>15</td>
<td>81</td>
</tr>
<tr>
<td>Frustration about your itching</td>
<td>6</td>
<td>17</td>
<td>77</td>
</tr>
<tr>
<td>Appearance of your skin from scratching</td>
<td>9</td>
<td>22</td>
<td>69</td>
</tr>
<tr>
<td>Feeling depressed about your itching</td>
<td>13</td>
<td>29</td>
<td>58</td>
</tr>
<tr>
<td>Feeling embarrassed about your itching</td>
<td>22</td>
<td>33</td>
<td>45</td>
</tr>
<tr>
<td>Effect of itching making it hard to work</td>
<td>23</td>
<td>33</td>
<td>45</td>
</tr>
<tr>
<td>Effects of itching on desire to be with people</td>
<td>32</td>
<td>33</td>
<td>35</td>
</tr>
<tr>
<td>Effects of itching on interactions with others</td>
<td>29</td>
<td>37</td>
<td>34</td>
</tr>
</tbody>
</table>
Figure Legends

**Figure 1:**
Extent to which patients report being bothered by itchy skin, by DOPPS phase
Footnote: Question wording: “To what extent were you bothered by itchy skin during the past 4 weeks?”

Footnote: (Australia, Belgium, Canada, China, France, the six Gulf Cooperation Council (GCC) countries (Bahrain, Qatar, Kuwait, Oman, Saudi Arabia, and United Arab Emirates), Germany, Italy, Japan, New Zealand, Russia, Spain, Sweden, Turkey, the United Kingdom, and the United States) were analyzed.

DOPPS Phase 1 collected data from 1996 to 2001; phase 2 from 2002 to 2004; phase 3 from 2005 to 2008; phase 4 from 2009 to 2011; and phase 5 from 2012 to 2015. Data collection in Australia, Belgium, Canada, New Zealand, and Sweden did not begin until phase 2; data collection in China began in phase 4 and started in GCC, Russia, and Turkey in phase 5. Australia, China, France, and New Zealand were excluded in phase 5.

**Figure 2:** Extent to which patients report being bothered by itchy skin in each country in DOPPS 5 (2012-2015).

Footnote: Ranked by proportion of patients who were moderately to extremely bothered by itchy skin.

Question wording: “To what extent were you bothered by itchy skin during the past 4 weeks?” 96% of patients answered this question among patients who completed a patient questionnaire.

ANZ = Australia and New Zealand, Bel = Belgium, Can = Canada, Chi = China, GCC = the six Gulf Cooperation Council countries (Bahrain, Qatar, Kuwait, Oman, Saudi Arabia, and United Arab Emirates), Ger = Germany, Ita = Italy, Jpn = Japan, Rus = Russia, Spa = Spain, Swe = Sweden, Tur = Turkey, UK = the United Kingdom, US = the United States of America.
Figure 3. The variation between countries in the practice of medical directors for referring patients with pruritus to a skin specialist or dermatologist. Data from 262 medical directors who returned their survey in 2013 (total N=337).

Footnote: Question text: “Among patients with pruritus, estimate the percent of patients you refer to a dermatologist or other specialist.”
Bel = Belgium, Can = Canada, GCC = the six Gulf Cooperation Council countries (Bahrain, Qatar, Kuwait, Oman, Saudi Arabia, and United Arab Emirates), Ger = Germany, Ita = Italy, Jpn = Japan, Rus = Russia, Spa = Spain, Swe = Sweden, Tur = Turkey, UK = the United Kingdom, US = the United States of America.
Figures

Figure 1:
Figure 2:
Figure 3.