

# NEPHROLOGY

# Rounds®

## Nephrocalcinosis, Oral Sodium Phosphate Solution, and Phosphate Nephropathy

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Nephrocalcinosis, a syndrome of renal parenchymal calcification, is associated with both acute and chronic kidney disease. Traditionally seen in patients with hypercalciuric disorders, medullary sponge kidney, or tumor lysis syndrome, recent reports have documented nephrocalcinosis following bowel preparation with oral sodium phosphate solution (OSPS), in a syndrome termed “phosphate nephropathy.” This preventable complication is not benign; one retrospective series revealed that 20% of patients progressed to endstage renal disease (ESRD) with variable degrees of chronic kidney disease (CKD) in the remainder. Safe and effective bowel preparation is challenging and OSPS, while effective and generally well tolerated, can induce hyperphosphatemia, hypokalemia, metabolic acidosis, and volume depletion, in addition to renal calcification. The Federal Drug Administration (FDA), plaintiffs’ attorneys, and the manufacturers of OSPS products have responded vigorously to the reports of kidney disease following OSPS. Although rare, internists, gastroenterologists, and nephrologists must be aware of this syndrome because it may be underdiagnosed and it is preventable by substituting OSPS with nonphosphate-containing preparative regimens in at-risk patients. This issue of *Nephrology Rounds* will address some of the gaps in our understanding of the incidence, risk factors, pathophysiology, and outcomes of phosphate nephropathy.

### Background: crystal deposition in the kidney

Renal crystal deposition is associated with a broad spectrum of acute and chronic kidney disease. The biochemical consequences of normal kidney function may promote crystal deposition, including supersaturation of solutes through urinary concentration or extremes of urinary pH.<sup>1</sup> Low urine flow, tubular injury, and other abnormal kidney conditions may also contribute to crystal formation. Medications, such as acyclovir, the sulfonamides, foscarnet, methotrexate, and indinavir are concentrated in the urine and can crystallize and deposit in the kidney.<sup>2</sup> More commonly, however, crystal deposition in the kidney parenchyma is associated with calcium, in conjunction with oxalate or phosphate, resulting in nephrocalcinosis. Hypercalciuria and hyperoxaluria are well-established risk factors for calcium crystal deposition.<sup>3,4</sup> Hyperphosphatemia can also cause nephrocalcinosis and may be under-appreciated as an etiology of both acute and chronic kidney disease in certain populations.

### Nephrocalcinosis

Nephrocalcinosis is usually detected radiographically, although pathologic examination is more sensitive. Plain films reveal “tiny flecks of calcium salts” in the calyces that resemble “pictures of the night sky.”<sup>5</sup> Computed tomographic (CT) urography provides superior sensitivity as compared to either plain films or renal ultrasound for diagnosis of nephrocalcinosis, with the classic appearance of deposits as bilateral clusters of medullary calcifications. In certain situations (eg, hyperparathyroidism), calcium salts are found along tubular basement membranes, as concretions within tubules, and as interstitial infiltrates. These lesions are usually found exclusively in the medulla, but may occur in the cortex or in the junction between the two,<sup>6</sup> accompanied by a sparse interstitial infiltrate. The functional consequences of these different crystal deposition patterns are poorly understood. Calcium-phosphate (Ca-Pi) deposits are detected in histology preparations by the *von Kossa* stain, which detects the phosphates; alizarin red detects the calcium. Ca-Pi crystals are not birefringent, whereas calcium-oxalate crystals are birefringent on microscopy using polarized light. Nephrocalcinosis reflects a primary pathophysiologic process or a severe tissue injury of any cause, so-called “dystrophic” calcification. Renal cortical necrosis, for example, can result in cortical calcifications that can be detected by KUB (plain radiograph of the kidneys, ureters, and bladder) several weeks after the initial insult and have been traditionally associated with non-recovery of renal function.<sup>6</sup>

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The molecular mechanisms underlying nephrocalcinosis are similar to those of nephrolithiasis, even though the two often occur independently. Ca-Pi deposition in the thin limb of Henle, where calcium and phosphate are supersaturated even under normal circumstances, may be the inciting event in the formation of Ca-Pi deposits called “Randall’s plaques.”<sup>1,7</sup> These plaques remain in the interstitium or rupture into the luminal space, where they serve as anchor sites for calcium-oxalate crystallization.<sup>8</sup> Ca-Pi crystals may also form within the urinary space and, particularly in the presence of hyperoxaluria, serve as a nidus for calcium-oxalate stone formation.<sup>7</sup> Alternatively, subsequent overgrowth of the urothelium and encapsulation of these crystals can result in nephrocalcinosis.<sup>3</sup> The observation that most calcium-oxalate stones contain some Ca-Pi is consistent with these proposed mechanisms of stone formation.<sup>1,5</sup> Despite these molecular similarities, clinical experience reveals that some patients with marked nephrocalcinosis have no stones, while others display the opposite pattern. Thus, the pathophysiology underlying these two conditions does not simply reflect different points of severity within the same spectrum of disease.<sup>9</sup>

Formation of Ca-Pi crystals is dependent on the ionic solubility product, which itself is dependent on temperature, ionic strength, pH, and calcium-phosphorus molar ratios. Citrate, Tamm-Horsfall protein, pyrophosphate, and other inhibitors of crystallization are critical to maintaining an “unstable compromise” of ionic supersaturation.<sup>10</sup> Not surprisingly, familial tubulopathies are characterized by hypercalciuria and frequently cause nephrocalcinosis, including cystic fibrosis, Bartter’s syndrome, and Liddle’s syndrome.<sup>3,11</sup> Once nucleated, crystal-crystal interactions can cause epitaxial stone growth in which urinary crystals of any type can promote formation of other types of crystals. This process explains why management of hyperuricemia can prevent calcium stone formation.<sup>12</sup>

### Clinical syndromes of calcium deposition

The clinical presentation of nephrocalcinosis is variable, from a benign condition diagnosed incidentally to that of a progressive tubulointerstitial process characterized by reduced glomerular filtration rate (GFR), a bland urine sediment, and minimal (<1 gram) proteinuria. Patients may present with renal colic, since nephrolithiasis often accompanies nephrocalcinosis. Hypercalcemic conditions, such as hyperparathyroidism, malignancy, granulomatous disorders, vitamin D intoxication, immobilization, and various medications, are the usual etiology. Distal renal tubular acidosis (RTA) may cause nephrocalcinosis through multiple mechanisms, including hypercalciuria and hypocitraturia secondary to intracellular acidosis. However, nephrocalcinosis itself can cause distal acidification defects that confound this association. Medullary sponge kidney is commonly associated with nephrocalcinosis, particularly in children.

Nephrocalcinosis can occur despite normocalcemia, particularly in the presence of hyperoxaluria. Patients with primary hyperoxaluria overproduce oxalate due to inherited enzyme defects and typically develop multiple kidney stones and eventually ESRD in young adulthood, as a result of both nephrocalcinosis and nephrolithiasis.<sup>4</sup> Similarly, nephrocalcinosis may result from calcium-oxalate deposition after acute ethylene glycol ingestion, since this compound is metabolized to oxalate.

## Phosphate and renal failure

Just as hyperoxaluria can drive calcium-oxalate deposition, hyperphosphatemia and hyperphosphaturia have been associated with nephrocalcinosis and renal failure in clinical settings marked by either exogenous phosphate therapy or endogenous phosphate release. Evidence from animal models also supports a direct role of hyperphosphaturia in the development of nephrocalcinosis and renal failure.

In the 1930s, and again in the 1960s, phosphate was used to treat symptomatic hypercalcemia of varying causes. Reports of metastatic calcifications and renal failure soon emerged.<sup>13-17</sup> Dudley and Blackburn used plain x-rays and slit lamp examinations to document extraskelatal calcifications in 4 patients who were normocalcemic at the start of phosphate therapy, two of whom developed renal insufficiency.<sup>18</sup> Clinical investigations confirmed that phosphate administration lowers serum calcium through Ca-Pi tissue deposition, although other mechanisms such as increased bone deposition have been proposed.<sup>19,20</sup>

Phosphate therapy has also been associated with nephrocalcinosis in patients with X-linked hypophosphatemic rickets (XLH) receiving calcitriol. Verge et al detected nephrocalcinosis by ultrasound in 19 of 24 such patients and correlated the mean dose of phosphate with the grade of nephrocalcinosis.<sup>21</sup> Alon et al reported kidney biopsy results on 3 children with treated XLH and documented Ca-Pi deposition by *von Kossa* staining.<sup>22</sup> Stickler et al reported 2 cases of renal failure requiring renal replacement therapy in treated XLH patients.<sup>23</sup> Other genetic conditions marked by hyperphosphaturia are associated with nephrolithiasis. Additionally, hypercalciuria may be present either idiopathically or, in some cases, as a result of a secondary increase in Vitamin D induced by low serum phosphate.<sup>24</sup>

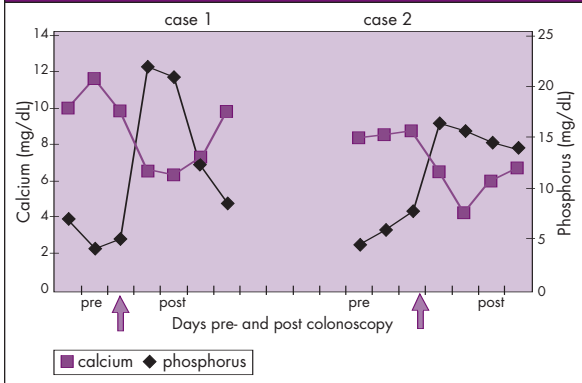
Acute renal failure (ARF) as a consequence of hyperphosphatemia is well described in the setting of tumor lysis, with documented Ca-Pi deposition in the tubules and tubular epithelium.<sup>25</sup> Boles et al reported a 15-year-old who developed dialysis-dependent ARF from Ca-Pi deposition in the setting of acute leukemia and summarized the literature of 34 similar cases.<sup>26</sup> Although alkalization of the urine to prevent uric acid nephropathy is commonly employed in tumor lysis syndrome, this maneuver may raise the risk of Ca-Pi deposition that occurs more readily at an alkaline pH. For this reason, many have argued that maintaining high urine flow with a neutral pH is the most important therapeutic strategy for the prevention and management of tumor lysis syndrome.

Animal studies also suggest that hyperphosphaturia, independent of hypercalciuria, can be important in the pathogenesis of nephrocalcinosis and renal failure. Hyp mice, a mouse model for XLH, develop nephrocalcinosis when treated with phosphate and Vitamin D. Additionally, Ritskes-Hoitinga et al observed nephrocalcinosis in rats fed a high-phosphate diet and demonstrated a protective effect of parathyroidectomy, male gender, and hypermagnesiuria.<sup>27,28</sup>

### Phosphate nephropathy associated with oral sodium phosphate solution

OSPS, used for bowel preparation prior to colonoscopy, commonly results in hyperphosphatemia and hyperphosphaturia. The acute rise in serum phosphorus following OSPS is well illustrated by 2 recent cases reported

**Figure 1: Graphic representation of electrolyte changes following oral sodium-phosphate solutions**

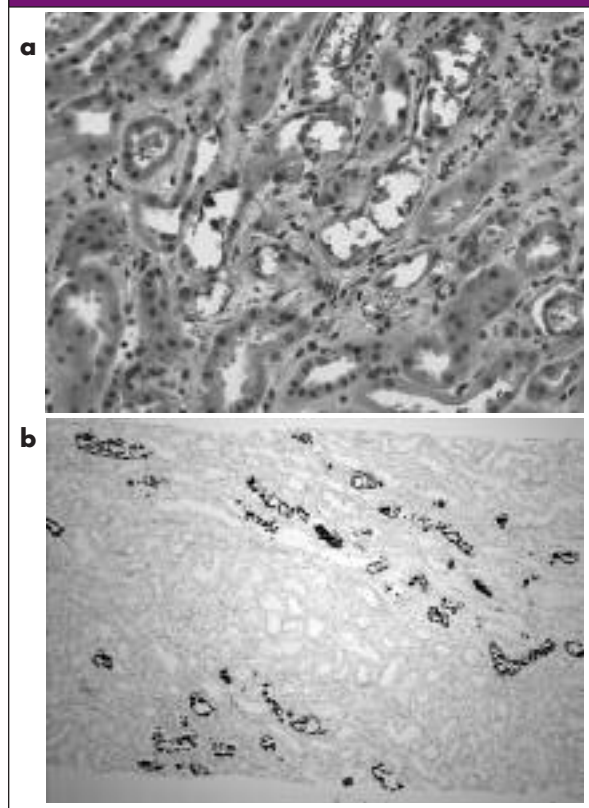


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by Mishra et al, and shown in Figure 1. Recent publications have documented the deposition of Ca-Pi within the kidneys of patients who have developed renal failure following OSPS, suggesting that the phosphate anion is driving the pathophysiologic process. In 2003, Desmeules and colleagues, in a letter to the *New England Journal of Medicine*, proposed the term “phosphate nephropathy” to describe the syndrome they observed in a 71-year-old woman whose creatinine rose from 1.0 to 4.5 mg/dL over a 10-week period following the use of a sodium phosphate-containing solution for colonoscopy.<sup>29</sup> Renal biopsy revealed numerous intratubular deposits positive for Ca-Pi by *von Kossa* staining. Analysis using scanning electron microscopy and x-ray microanalysis confirmed the deposits to be calcium and phosphate in the form of hydroxyapatite crystals. The patient had a persistent elevation in creatinine above baseline 1 year later, suggesting long-term kidney damage. Earlier, Orias and co-workers reported a 76-year-old who developed hyperphosphatemia and dialysis-dependent ARF after receiving 5 phosphosoda enemas. However, Ca-Pi deposition was not documented, since no renal biopsy was performed.<sup>30</sup>

In 2004, Markowitz and colleagues at Columbia University described 5 patients who developed renal failure following OSPS.<sup>31</sup> Kidney biopsies, performed in all patients at different times relative to the OSPS administration, revealed diffuse tubular injury (ranging from acute tubular necrosis to more chronic tubular changes) and distal tubular Ca-Pi deposits. Figure 2 demonstrates typical kidney biopsy findings in phosphate nephropathy, with tubular crystal deposition visible on *H&E* stain and dark black calcium phosphate crystals revealed on *von Kossa* staining. Subsequently, Markowitz and co-workers reviewed 7,349 native kidney biopsies processed at their center and identified 31 patients whose biopsies included significant Ca-Pi deposits.<sup>32</sup> Among these, 16 patients (in addition to the 5 reported previously) met the authors’ definition of acute phosphate nephropathy: they had developed ARF soon after colonoscopy with an OSPS preparation and were normocalcemic (OSPS may have contributed to kidney injury in half of the remaining 10 patients as well). The 21 patients had a mean age of 64 years and had good renal function at baseline (17 of 21 had a baseline creatinine <1.2 mg/dL). In addition, 14 of 21 were receiving an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker

**Figure 2: Biopsy findings in phosphate nephropathy: a, tubular crystal deposition; b, calcium-phosphate crystal deposition (black)**



(ARB) and several were on diuretics or nonsteroidal anti-inflammatory drugs (NSAIDs) as well. Ca-Pi deposits were present in the distal tubules of the cortex and medulla, predominantly within tubular epithelial cells and lumina, with less involvement of the interstitium. Follow-up at a mean of 16.7 months revealed the phosphate-associated kidney injury to be largely irreversible; 4 of the 21 patients had become dialysis-dependent and the majority had CKD, with a mean serum creatinine of 2.4 mg/dL. In January 2006, Gonlusen and colleagues reported another case of apparent phosphate nephropathy in a 56-year-old following OSPS.<sup>33</sup>

The mechanism by which OSPS-induced hyperphosphatemia causes kidney failure is likely multifactorial. Ca-Pi deposition may be a primary pathophysiologic event. Alternatively, tubular injury from other causes may result in dystrophic calcification. In either case, Ca-Pi deposits appear to cause long lasting tubular damage proceeding to nephron loss and fibrosis. Other pathophysiologic mechanisms may exist. In a rat model of nephrotoxic and ischemic renal injury, Zager demonstrated that hyperphosphatemia potentiated renal damage by inducing proximal tubular vacuolization and glomerular capillary collapse, without evident nephrocalcinosis.<sup>34</sup> Risk factors for OSPS-associated ARF have not been rigorously defined, but are shown in Table 1. These risk factors include excessive dose; retention of OSPS due to poor bowel motility or colitis; baseline volume depletion; diuretic, ACEI, ARB, and NSAID use; congestive heart failure; ascites; and advanced age.<sup>32,35,36</sup> Importantly, OSPS can induce volume depletion, dehydration, and severe electrolyte disturbances that may cause or

**Table 1: Putative phosphate nephropathy risk factors**

- Acute or chronic kidney disease
- Prior renal transplant
- Advanced age
- Female gender
- Hypertension
- True volume depletion
- Effective volume depletion
- ACEI, ARB, diuretic, or NSAID use
- Abnormal bowel motility
- Excessive / Repeated OSPS Dosing

contribute to the tubular injury, independent of calcium and phosphate. The range of metabolic abnormalities that have been associated with OSPS is usefully discussed in the context of bowel preparation in general.

### The challenge of bowel preparation

The challenge of cleansing the colon safely, effectively, quickly, comfortably, and affordably is not a trivial one. Prior to the 1980s, enemas consisting of castor, senna, bisacodyl, or other substances were used and were associated with significant cramping. Attempts to use mannitol as an osmotic agent were stymied by the fermentation of the sugar into flammable hydrogen gas, with reports of intraoperative colonic explosions.<sup>37</sup> Balanced electrolyte lavage solutions effectively clean the bowel, but their use results in significant net fluid and electrolyte absorption. Fordtran and colleagues at Baylor solved this problem by combining nonabsorbable sodium sulfate with polyethylene-glycol and coined the term ‘GoLytely’ to describe what is more generally referred to as polyethylene-glycol electrolyte lavage solution (PEG-ELS).<sup>38</sup> A version without sodium sulfate, known as Nu-Lytely, became available in 1990.<sup>39</sup> Despite the demonstrated effectiveness and safety of PEG-ELS, many patients are troubled by the taste and the 4-litre volume they must ingest. Efforts to devise more palatable bowel preparations continue, most recently manifest in the use of half-dose Nu-Lytely (2L rather than 4L) in combination with bisacodyl tablets (called Half-Lytely). It was the search for alternatives to standard PEG-ELS preparations that led back to OSPS, which had been available for many years. In early studies comparing the two, many patients and colonoscopists preferred OSPS.<sup>40-42</sup>

Like magnesium hydroxide (milk of magnesia) and lactulose, OSPS is an osmotic purgative that obligates water excretion into the intestinal lumen to maintain its isotonicity with plasma.<sup>43</sup> OSPS is hyperosmolar due to its high sodium and phosphate content. Each 45 mL dose of Fleet® Phospho-soda® contains 5 g of sodium and 17.8 g of phosphate, with a total of 748 mOsm.<sup>43</sup> Two sodium phosphate tablet preparations are also available: Visicol®, which is similar in content to Fleet® Phospho-soda, and Osmo-Prep®, which contains approximately 25% less phosphate. These preparations lead to both sodium and phosphate absorption,

as well as osmotically-driven luminal water excretion. The content of OSPS is such that, if phosphate absorption did not occur, a 100 mL dose would obligate 4.1 liters of stool.<sup>44</sup>

Metabolic disturbances, including hyperphosphatemia, hypocalcemia, hypernatremia, hypokalemia, and metabolic acidosis, have been recognized complications of OSPS for many years; these are sometimes accompanied by volume depletion and ARF, which is usually attributed to hemodynamic insult.<sup>45-47</sup> Adults with normal renal function reliably develop hyperphosphatemia after OSPS ingestion, with one study reporting a rise in the mean serum phosphate from 3.7 to 7.3 mg/dL.<sup>36,40,48</sup> Ca-Pi products in excess of 65 were seen in 36% of normal volunteers in another study.<sup>49</sup> Severe hyperphosphatemia and hypocalcemia with tetany have been reported in patients with both abnormal and normal renal function.<sup>35,50,51</sup> Particularly severe electrolyte disturbances and deaths are associated with abnormal gut motility (predisposing to enhanced phosphate absorption), excessive dose, and advanced age.<sup>52-55</sup> Each 45 mL dose of OSPS is associated with the loss of 1 to 1.8 L of (hypotonic) fluid and thus, dehydration, volume depletion, and hypernatremia are not uncommon.<sup>44,49,56</sup> Electrolyte disturbances from OSPS have been associated with delayed recovery from general anesthesia and central pontine myelinolysis.<sup>47,57</sup> Significant anion-gap acidosis has been described, with phosphate serving as the unmeasured anion.<sup>58</sup>

The potential for electrolyte disturbances with OSPS led some authors to warn against their use early on, particularly in patients with kidney, cardiac, or liver disease.<sup>59,60</sup> In 2001, the FDA reviewed the safety of oral sodium phosphate and issued a report urging physician awareness, and suggesting the verification of electrolytes in high-risk patients.<sup>61</sup> Despite these warnings, new cases continue to be reported. This has prompted a group in Hong Kong, who observed symptomatic hypocalcemia in a patient with normal renal function, to term OSPS “a forgotten menace.”<sup>62</sup>

### Government, legal and industry response

Over 14 million colonoscopies are performed in the USA each year and efforts to increase screening rates have included well-publicized celebrity endorsements.<sup>63,64</sup> Not surprisingly, the reports of renal failure in association with oral sodium phosphate resulted in vigorous responses from interested and responsible parties. In May 2006, the FDA issued an alert noting the association, insisted that changes be made to the relevant prescribing information, and published a scientific background paper ([www.fda.gov/cder/drug/infopage/osp\\_solution](http://www.fda.gov/cder/drug/infopage/osp_solution)). Multiple media reports appeared on the subject and the consumer advocacy group, Public Citizen, added sodium phosphate preparations to its “worst pills” website, [www.worstpills.org](http://www.worstpills.org). Plaintiffs’ attorneys began to advertise on television and troll the Internet for cases; in some instances, they offered free consultations with a lawyer “if you have had a colonoscopy, radiological procedure, or surgery,

and have developed kidney failure” (www.pritzkerlaw.com/Phosphate\_Nephropathy/).

The C.B. Fleet Company detailed the professional labeling changes in two “Dear Doctor” letters sent to U.S. physicians in February 2005 and May 2006 (<http://www.phospho-soda.com/professionals/default.aspx>). These letters reported that, in addition to the published reports, the company had been made aware of 10 additional spontaneous reports of renal failure and nephrocalcinosis in 2005. The Company halted the sale of all but the 45 mL bottle of OSPS, to avoid the accidental overdose that occurred when larger bottles were prescribed, and introduced new retail packaging with clearer instructions. The company funded a study (as yet unpublished), which reportedly demonstrated that rats fed a high-phosphate diet developed nephrocalcinosis only when pre-existing ischemia/reperfusion injury and dehydration were present. The company also convened a panel of experts who concluded in April 2006 that, while the true incidence of nephrocalcinosis associated with OSPS is unknown, the frequency appears “very low” and the benefit/risk profile of OSPS “remains favorable.”<sup>65</sup> The panel advised clinicians to avoid OSPS in patients with CKD and those at risk for dehydration. They further recommended that no more than two 45 mL doses be prescribed, separated by 6–12 hours, and accompanied by at least 64 oz (2 L) of fluid intake. However, as the FDA points out, recommendations for volume repletion with OSPS vary from 0.7 to 2.2 liters (Fleet itself recommends 72 oz) and the actual volume necessary to control electrolytes and prevent phosphate nephropathy is unknown.<sup>66</sup>

### Future directions

There are significant gaps in our knowledge of nephrocalcinosis and phosphate nephropathy. Prospectively collected data concerning putative risk factors such as hypertension, female gender, and ACEI/ARB use would be particularly helpful. The true incidence is unknown and may remain so, pending the assessment of noninvasive methods such as CT imaging or slit-lamp examination to make the diagnosis of nephrocalcinosis.<sup>18</sup> The role of parathyroid hormone, vitamin D, and phosphatonins in the pathophysiology of phosphate nephropathy remains completely undefined, as does the role of potential inhibitors, such as citrate, fetuin-A, and matrix Gla protein.<sup>67,68</sup> The pathophysiologic mechanisms that result in nephrocalcinosis rather than nephrolithiasis also need better definition.

### Conclusions

Phosphate nephropathy is an important and probably under-appreciated cause of acute and chronic kidney disease. Multiple causative factors may contribute, especially in patients with impaired intrarenal hemodynamics at baseline or volume depletion (exacerbated or caused by OSPS). Adequate volume repletion may reduce the risk associated with OSPS. Clinicians selecting bowel-cleansing agents must consider the many metabolic consequences of OSPS use and prescribe agents in well-selected subjects. Adequate bowel preparation is mandatory for colorectal cancer screen-

ing and the renal risks posed by OSPS raised in this article should not change clinical practice in the vast majority of patients. Nonetheless, the ethical imperative to “do no harm” and the large and growing number of colonoscopies performed each year compel physicians to favor bowel purgatives that pass a very high standard of safety. Nephrologists need to be aware of phosphate nephropathy so they can diagnose patients with the characteristic findings, as well as appropriately advise primary care physicians and gastroenterologists on the management of CKD and other at-risk patients who require colonoscopy. Ongoing use of OSPS in inappropriate patients, despite literally hundreds of published adverse reactions, highlights serious shortcomings in prescribing practices and underscores the limitations of the extant medical literature in improving patient safety.

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