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Original Article

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Management of Common Medical Conditions in End-Stage Kidney Disease by the General Practitioner

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ABSTRACT

Objective: Patients with end-stage kidney disease (ESKD) represent a clinical challenge when it comes to the management of certain medical problems, and successful management of these patients requires substantial knowledge of their unique condition. This article presents a review of some aspects of ESKD that are less clear among general practitioners.
Methods: We conducted a clinical survey for 200 physicians and practitioners in a community hospital setting to explore how general practitioners would manage certain medical problems in ESKD patients.
Results: 75% of respondents considered intravenous fluid administration for the treatment of diabetic keto-acidosis in anuric ESKD patients although they are protected from hypovolemia resulting from osmotic diuresis; 47% considered potentially nephrotoxic agents safe in peritoneal dialysis patients with residual kidney function; and 31% chose immediate dialysis following the exposure to an intravenous iodine contrast in anuric ESKD patients. We searched the literature for the available evidence in the management of these issues along with other medical problems that general practitioners encounter.
Conclusion: Certain concepts in ESKD maybe less clear among general practitioners: 1) Anuric ESKD patients with diabetic hyperglycemic emergencies are protected from osmotic diuresis-induced hypovolemia; 2) Peritoneal dialysis patients with residual kidney function should not be treated similar to anuric ESKD patients in regards to nephrotoxic agent administration; and 3) Intravenous iodine contrast carries no potential risk in anuric end-stage kidney disease patients and immediate removal by dialysis is not warranted. Successful management of ESKD patients requires substantial knowledge of their unique condition and effective communication between medical staff and nephrologists.
Keywords: Contrast-induced nephropathy, end-stage kidney disease, nephrotoxic agents, peritoneal dialysis, residual kidney function

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INTRODUCTION

End-stage kidney disease (ESKD) remains a worldwide public health problem. According to the United States Renal Data System (USRDS) 2019 Annual Data Report, the number of prevalent ESKD cases has continued to rise by about 20 000 cases per year, reaching 746 557 prevalent cases in December 2017, with a crude prevalence of 2205 cases per million in the USUS) population. The incidence of ESKD, on the other hand, has been stable since 2015.[1]

Diabetes mellitus (DM) and hypertension are the most common causes of chronic kidney disease (CKD) and ESKD, both in the USA[1] and globally.

Several aspects in the management of patients with ESKD have been addressed and well taken care of according to the best available high-quality evidence and society guidelines,[2] including the treatment of fluid overload, CKD-related anemia, hyperkalemia, CKD-mineral and bone disorder, and so on. On the other

hand, a few issues that are common to the general practitioners, including hospital medicine physicians, physician assistants, and emergency care providers, have not been well addressed. A high-quality evidence or specific guidelines may be lacking in the management of these issues that will be discussed in this review.

The following medical conditions and situations will be discussed here in detail.

1. Fluids management in diabetic hyperglycemic emergencies in anuric ESKD.
2. The concept of residual kidney function and nephrotoxic agents administration.
3. Iodine contrast exposure and risk of toxicity in anuric ESKD.
4. High-risk medication management in ESKD.
5. Antibiotics management in ESKD.
6. Diagnosis and treatment of peritonitis in peritoneal dialysis (PD).

Of note, ESKD patients on renal replacement therapy represent a unique patient population and should not be treated similarly to patients with CKD who are not on renal replacement therapy yet.

METHODS

The authors conducted an anonymous 4-question clinical survey which was randomly distributed to internal medicine practitioners and intensive care providers in a community hospital setting. The goals of the survey were clearly explained to survey respondents, which included improving the clinical practice and management of certain medical problems commonly encountered in ESKD patients.

The first question was about the provider's specialty: internal medicine, intensive care, nephrology, or other.

The second question was about the options of the management for a 50-year man with ESKD on hemodialysis (HD) who is anuric and is presenting with diabetic ketoacidosis (DKA) and hyperosmolar state without vomiting and with normal potassium level. Options included were insulin and intravenous fluids, insulin only, or intravenous fluids only.

The third question was about a patient with ESKD on PD who has a urine output of 900 mL per day and is presenting with acute non-resolving pancreatitis that requires a computed tomography with iodinated contrast media (ICM) to assess for complications. The patient was also requesting a non-steroidal anti-inflammatory drug (NSAID) for his pain. Options included were given as follows NSAID and ICM are safe since the patient is on dialysis, NSAID and ICM are unsafe since the patient has an adequate residual kidney function (RKF), or NSAID and ICM are safe since the patient may have inadequate RKF.

The fourth question was whether or not the provider will arrange for immediate dialysis following ICM exposure in an anuric patient with ESKD. Options included were yes or no.

RESULTS

In total, 200 providers responded to the survey. Figure 1 shows the specialty of respondents. The majority were internal medicine practitioners (55%), then intensive care providers (17%), and then nephrologists (8%). Other specialties were 20%.

Figure 2 presents the answers to question number 2: 75% have considered intravenous fluids, with or without insulin, for an anuric ESKD patient with DKA and hyperosmolar state. Only 24% have considered insulin.

Figure 3 presents the responses to question 3: 47% have considered it safe to administer NSAID and ICM to a patient on PD who has a 900 mL daily urine output, either because his RKF is thought to be inadequate or because he is already on dialysis and 49% considered it unsafe to administer NSAID or ICM because of the adequate RKF.

Figure 4 shows the answers to question 4: 31% considered an immediate HD following ICM exposure for an anuric ESKD patient and 66% did not consider an immediate HD in this scenario.

MAIN POINTS

- End-stage kidney disease (ESKD) patients on kidney replacement therapy represent a unique patient population and should not be treated similarly to patients with chronic kidney disease who are not on kidney replacement therapy yet.
- The importance of residual kidney function should be emphasized and measures to preserve it should be applied in patients with ESKD who still have urine, particularly those on peritoneal dialysis.
- General medicine practitioners should always consult with nephrology specialists when it comes to issues that lack clear guidelines or specific recommendations.

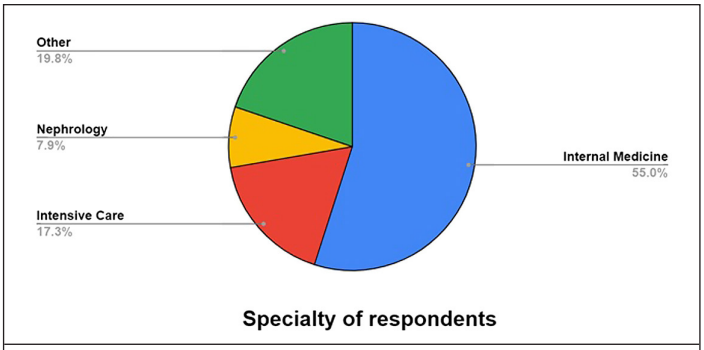

Figure 1. Specialty of respondents.

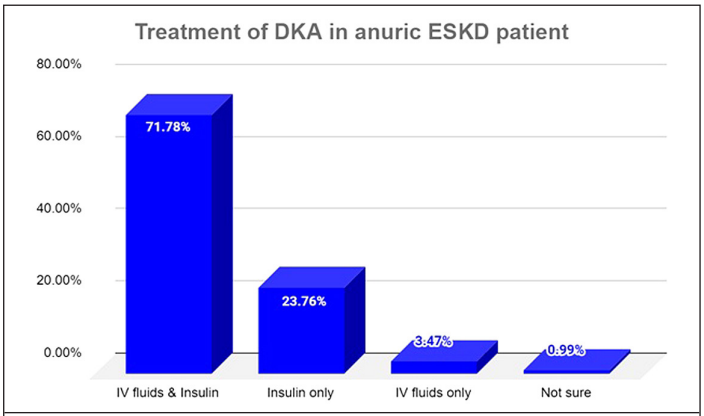

Figure 2. Treatment of DKA in anuric ESKD patient. ESKD, end-stage kidney disease; DKA, diabetic ketoacidosis.

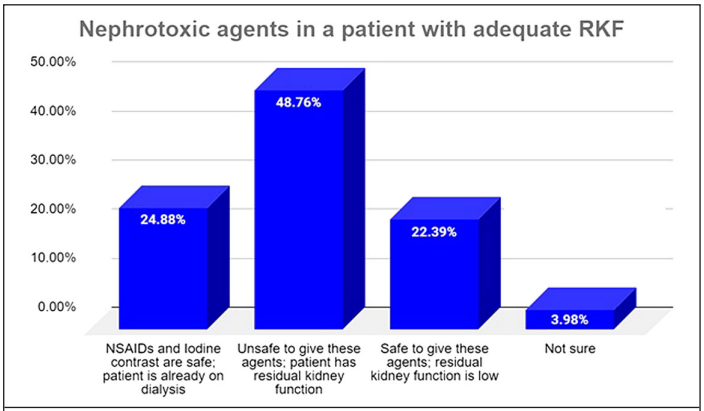

Figure 3. Nephrotoxic agents in a patient with adequate RKF. RKF, residual kidney function.

DISCUSSION

Fluids Management in Diabetic Hyperglycemic Emergencies in Anuric End-Stage Kidney Disease

Diabetes is a leading cause of ESKD, with about half of patients requiring dialysis having a diagnosis of diabetes.

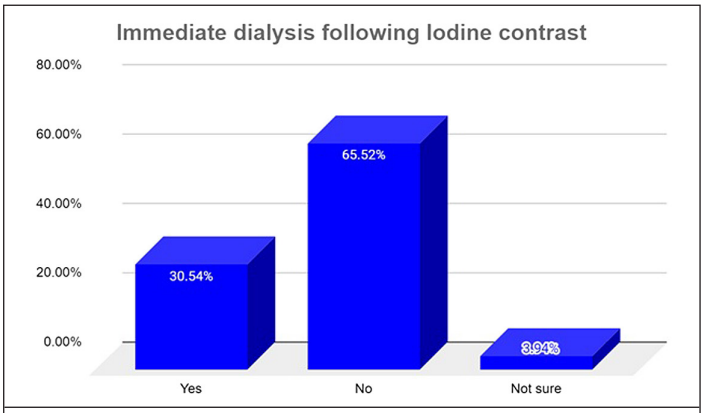

Figure 4. Immediate dialysis following iodine contrast.

Clinical presentation and management of KDA and hyperosmolar hyperglycemic state (HHS) are unique in ESKD patients, particularly anuric individuals. In patients who are anuric, absence of glycosuria and the subsequent osmotic diuresis results in severe hyperglycemia since glucose is not being lost through the kidneys. However, severe hyperosmolality with accompanying alteration of mental status is unusual because of the absence of water loss induced by osmotic diuresis. Thus, even extreme hyperglycemia is often asymptomatic in ESKD patients.[3] Hypervolemia manifested occasionally by pulmonary edema and weight gain may happen in such settings due to absence of water and solute diuresis in patients with hyperglycemia, in contrast to hypovolemia in patients with normal kidney function who develop DKA or HHS.[4,5]

Several reports evaluated the differences in clinical characteristics and outcomes of hyperglycemic emergencies in ESKD patients compared to patients with normal renal function. Galindo et al[6] showed that the ESKD group with DKA has two-fold higher glucose levels and ten-fold rates of fluid overload compared with DKA in patients with preserved kidney function. The need for mechanical ventilation and length of hospital stay were also higher among ESKD group.

Clinical practice guidelines for insulin management in CKD exist, but no such official recommendations exist for insulin or fluid management in hyperglycemic emergencies in anuric ESKD individuals.

Some healthcare providers may be misled and manage anuric ESKD patients with hyperglycemic emergencies in a similar fashion to patients with normal renal function in terms of aggressive fluids administration**.** This was illustrated by the results of our clinical survey of 200 medical providers, mainly internists and intensivists, which showed that 75% would administer intravenous fluids, with or without insulin, to anuric ESKD patient with DKA who has no vomiting or other source of fluid loss (figure 2). This may lead to worse outcomes in this patient population when being treated for DKA, like fluid overload, pulmonary edema, higher mortality and length of stay, and the need for urgent dialysis.

Proposals to improve knowledge and practice:

Diabetic ketoacidosis is usually managed through a built-in algorithm and/or a clinical decision support system (CDSS) in the computerized physician order entry (CPOE) to guide the treating healthcare provider. So, the management of ESKD patients can be guided by a screening question that asks whether the patient has anuric ESKD when it comes to fluids order. If the answer is yes, then a message appears that notify the ordering provider that no fluids are needed, and the treatment is going to be by administering insulin only.

The Concept of Residual Kidney Function and Nephrotoxic Agents Administration

Residual kidney function is defined as the remaining kidney function in patients receiving renal replacement therapy, and it reflects the ability of the native kidneys to eliminate water and uremic toxins.

The importance of RKF is well established in PD. Numerous studies demonstrated that RKF is an extremely important determinant of mortality and morbidity in PD patients and is associated with better survival, quality of life, nutritional status, and phosphorus control, with reduced inflammation, erythropoietin requirements, blood pressure, and left ventricular hypertrophy.[7,8]

The importance of RKF is becoming increasingly recognized in the HD population, and many studies showed that RKF is correlated with better survival, quality of life, and nutritional status in HD patients.[9]

Strategies to preserve RKF in this patient population, such as avoiding nephrotoxic agents among other measures, are critical to improve mortality, morbidity, and quality of life for individuals on renal replacement therapy.

Some healthcare providers might not be fully aware of the concept of RKF, particularly in PD patients, and assume that patients on dialysis are all the same, or that being on dialysis indicates that the renal function is always null. This misconception was revealed by the results of our clinical survey of 200 medical providers, mainly internists and intensivists, which showed that 47% will administer a nephrotoxic agent, such as NSAIDs, to a patient on PD with RKF because the patient is already on dialysis or because of misinterpretation of his RKF (Figure 2).

Proposal to Improve Practice

For every patient with ESKD, particularly on PD, a prompt evaluation of daily urine output should be part of the initial nursing assessment and a chart alert should be raised to alarm the healthcare providers about the importance of preserving the patient's RKF if urine output was determined to be adequate. Strategies to preserve RKF will be detailed in the chart alert. This is a form of CDSS.

Contrast Exposure

The use of intravenous ICM is important in many diagnostic testing and angiographic studies or procedures. Iodinated contrast media-induced systemic injury encompasses a variety of systemic disorders, the most recognizable are the nephrotoxic effects including contrast-induced nephropathy (CIN) and less likely, volume overload or hypertension. The frequency of adverse reactions significantly reduced with the current use of non-ionic low-osmolar contrast media.

Patients with pre-existing kidney disease and DM remain at the highest risk for the development of CIN.[10]

The majority of studies on CIN in patients with normal baseline kidney function lacked proper control groups and patients received ionic high-osmolarity contrast agents which are no longer in use.

Several recent studies demonstrated no correlation between acute kidney injury and the use of low-osmolarity or isosmolar ICM in patients with normal creatinine values,[11] or a baseline creatinine $\geq$ 1.3 mg/dL in one study.[12]

Regarding patients with ESKD on kidney replacement therapy (KRT), the question in clinical practice is: Are these patients at risk of adverse effects of ICM?

Some healthcare providers may consider immediate dialysis following the exposure to ICM in a patient with ESKD maintained on regular HD to decrease the risk of adverse reactions. This was illustrated by the results of our clinical survey of 200 providers, mainly internists and intensivists, which showed that 31% selected "yes" to immediate dialysis following ICM exposure in this situation (Figure 3).

Two major concerns arise in patients with ESKD on KRT:

1) Preservation of RKF.
2) Avoidance of fluid overload by a relatively high-osmolar ICM or other toxic effects of ICM exacerbated by underlying kidney disease.

Point 1

In ESKD patients who still have RKF, avoiding nephrotoxic agents such as ICM to preserve RKF, as was emphasized in the previous section, is crucial to improve mortality, morbidity, and quality of life in ESKD patients, particularly in PD. So, such patients should only receive ICM if it is critically indicated (e.g., percutaneous coronary intervention in acute myocardial infarction).

Point 2

Four studies suggested the safety of low-osmolar ICM in ESKD patients maintained on HD; none of the studied patients developed a serious adverse effect or required an urgent session of dialysis post-ICM exposure.

Of these 4, 2 small studies showed that ICM administration was not associated with significant changes in blood pressure, electrocardiography, serum osmolality, bodyweight or volume status, or clinical features that necessitated urgent or earlier HD occurred in patients maintained on KRT.[13,14] A third small cohort of 22 patients also showed no side effects of ICM administration after 5 days in hemodialyzed ESKD patients when compared to individuals with normal renal function.[15]

The fourth study included 1287 patients undergoing chronic HD and showed that ICM administration was not associated with adverse effects, and none of the patients required HD before the next routine scheduled session.[16]

Even for patients with CKD not on dialysis, a prophylactic KRT after ICM exposure did not decrease the risk of CIN compared to standard therapy (i.e., intravenous fluids) although HD and PD can efficiently remove ICM from the bloodstream and systemic circulation. This was demonstrated by the systematic review with meta-analysis, by Cruz et al.[17] that pooled results from 11 trials that examined the efficacy of prophylactic periprocedural KRT in reducing the risk of CIN. Indeed, HD was associated with an increased risk of CIN when the analysis was limited to HD studies only, with a relative risk (RR) of 1.61 [1.13-2.28]. This paradoxical increase in CIN in the HD groups is not fully understood.

Finally, the Contrast Media Safety Committee of the European Society of Urogenital Radiology states that there is no need to schedule the dialysis in relation to the injection of contrast media or the injection of contrast agent in relation to the dialysis program.[18]

Proposal to Improve Practice

A clinical decision support tool can be applied. An alert message notifies the ordering provider that no immediate dialysis is warranted if the anuric ESKD patient requires a contrast study using ICM.

High-risk Medication Management in ESKD

Management of high-risk medications in ESKD patients includes the appropriate drug dosage for HD and PD, proper drug selection, considering the proper indications and contraindications in ESKD, drug interactions, drug adverse effects, and special considerations to the adverse cardiovascular effects of certain medications given the high cardiovascular morbidity among ESKD patients.

In the current era of electronic medical systems and the CPOE, adjusting medications to meet the needs of this population should be a standard practice.[19]

We present the following high-risk medications and the contraindicated drugs in each class. We discuss the common practices we encountered that need special attention.

Opioids

Morphine is one of the most commonly used inpatient opioid analgesics. Very often, this is used in ESKD patients although it should be avoided because of the accumulation of active metabolites and their rebound effect.[20] Of note, even the opioid agents that need no dose reduction still require extreme caution when used in this patient population.[21-23] Table 1 summarizes the analgesic drugs including opioids that should be avoided in ESKD patients.

Neuropathic Pain Treatment

Among the prevalent medications for neuropathic pain is gabapentin, which is an anticonvulsant GABA analog and is reported to cause neurologic toxicities in ESKD patients. This may result from failure to adjust its dose with advancing renal insufficiency.[24,25] Table 1 summarizes the analgesic drugs that should be avoided in ESKD patients.

Benzodiazepines

Benzodiazepines (BZD) use in ESKD patients is associated with increased mortality. This was demonstrated by studies in the US and in Japan.[28,29]

Table 1. Management of High-Risk Pain Medications in ESKD Patients

Opioids			**Neuropathic Pain Treatment**[26,27]		
Avoid	**Adjust Dose**	**No Dose Reduction**	**Avoid**	**Adjust Dose**	**No Dose Reduction**
Morphine	Methadone (50% of usual dose)	Buprenorphine	Duloxetine	Gabapentin (max 300 mg/ day)	Carbamazepine
Codeine	Fentanyl patch (50% of usual dose)	Fentanyl (except patch)	ER pregabalin	IR pregabalin (max 75 mg/ day, extra post-HD dose)	Nortriptyline
Meperidine	IR Hydromorphone (25% of usual dose)	Alfentanil		Venlafaxine (50% of usual dose)	Amitriptyline
Oxycodone	IR Tramadol (initial 25 mg q12h, max 50-200 mg/day)				
ER hydromorphone					
ER tramadol					

ER, eExtended-release formulation; HD, hemodialysis; IR, immediate release; mg, milligrams; q12h, every 12 hours; ESKD, end-stage kidney disease.

Table 2. Management of Antianxiety Medications in ESKD Patients

Antidepressants/Antianxiety[35-37]			Benzodiazepines		
Avoid	**Adjust Dose**	**No Dose Aadjustment**	**Avoid**	**Adjust Dose**	**No Dose Adjustment**
Duloxetine	Paroxetine IR or ER (50%)	Fluoxetine	Diazepam	Chlordiazepoxide (50%)	Clonazepam (may accumulate)
Milnacipran	Citalopram (50%)	Sertraline	Flurazepam	Midazolam (50%)	Clorazepate
Levomilnacipran	Venlafaxine (50%)	Escitalopram	Clorazepate	Parenteral lorazepam	Flurazepam
Selegiline	Desvenlafaxine (50%)	Fluvoxamine			Oral lorazepam
Phenelzine	Mirtazapine (50%)	Trazodone, nefazodone			Oxazepam
Buspirone	Bupropion	Tricyclic antidepressants[a]			Temazepam, triazolam

[a]Caution (cardiac toxicity).
ESKD, end-stage kidney disease.

Although the majority is hepatically metabolized, some BZD need careful monitoring or dose adjustment in ESKD patients.[30] Librium, for example, is commonly used in general medicine for the prevention of alcohol withdrawal and it needs a 50% dose reduction. Intravenous lorazepam may cause propylene glycol toxicity if used for prolonged periods.[31] Benzodiazepines with active metabolites such as chlordiazepoxide, diazepam, flurazepam, and clorazepate should be avoided in patients with renal insufficiency and patients with ESKD.[32-34] Table 2 summarizes the anti-anxiety medications in ESKD.

Muscle Relaxants

Baclofen is a commonly used skeletal muscle relaxant that works centrally at the spinal cord level. It has been reported to cause encephalopathy and neurotoxicity in CKD and ESKD patients.[38,39] Table 3 summarizes the use of all muscle relaxants in ESKD, in addition to antipsychotics.

Antibiotics

The use of antibiotics in ESKD patients on dialysis is a broad subject and requires a separate review; nevertheless, a few concepts that are unique to ESKD patients deserve special attention by the general practitioners in daily practice:

1. Patients who receive antibiotics after each HD session who may undergo an irregular schedule (i.e., extra sessions or missing sessions) might be undertreated if the antibiotics were not administered in conjunction with the exact dialysis schedule. For example, if a patient receives an extra session of HD on top of his thrice weekly schedule, who is on an antibiotic dosed thrice weekly after HD sessions, a dose will most likely be missing if the extra HD was not followed by an additional antibiotic dose.[42]
2. For antibiotics that are administered during the last 1 hour of HD, consideration should be taken to the fact that clearance of medications is higher than when they are given after HD,

Table 3. Management of Muscle Relaxants and Anti-Psychotics in ESKD

Muscle relaxants			Anti-Psychotics/Anti-Manic[40,41]		
Avoid	**Adjust Dose**	**No Dose Reduction**	**Avoid**	**Adjust Dose**	**No Dose Reduction**
Baclofen	Tizanidine	Cyclobenzaprine	Paliperidone	Lurasidone (50%, max 80 mg/day. ND)	Clozapine
Metaxalone		Methocarbamol	Cariprazine	Risperidone (50%)	Olanzapine
		Carisoprodol	Lithium		Quetiapine
		Chlorzoxazone			Ziprasidone
		Orphenadrine			Iloperidone
					Brexpiprazole
					Pimavanserin
					First-generation antipsychotics

ND, non-dialyzable; ESKD, end-stage kidney disease.

Table 4. Antibiotics That Require No-Dose Adjustment in ESKD

Penicillin V potassium	Moxifloxacin	Paromomycin
Penicillin G procaine	Doxycycline	Quinupristin and dalfopristin
Penicillin G benzathine	Eravacycline	Linezolid[a]
Cefaclor[a]	Sarecycline	Tedizolid
Ceftriaxone (use of >2 g/day has not been studied)	Omadacycline	Azithromycin
Oral vancomycin	Clindamycin	Erythromycin

[a]Supplemental dose post HD is needed.
ESKD, end-stage kidney disease.

particularly for highly dialyzed drugs (i.e., more than 30%). A higher dose will most likely be needed, otherwise, undertreatment of the infection may occur as a result. In one study, vancomycin infused to dialyzed patients during the last hour of the dialysis session at increased doses (1.4 g) was effective in infection control, achieved recommended concentrations despite the use of high-flux membranes, and improved patients' quality of life.[43] Table 4 shows the antibiotics that require no dose adjustment in ESKD.

3. Antibiotics-induced neurotoxicity in ESKD patients: cephalosporins particularly ceftazidime and cefepime, carbapenems, acyclovir, and isoniazid among others were reported to cause neurotoxicity in ESKD patients at a higher rate than other patients.[44]
4. Inappropriate use of antibiotics: failure to promptly discontinue antibiotics based on negative culture results to avoid potential adverse effects. Although this should apply to all clinical settings, ESKD patients are at a significantly higher risk of toxicity given their complex metabolic derangement and also, failure to switch antibiotics from vancomycin to β-lactams or from third and fourth generation cephalosporins to cefazolin when appropriate. Studies of methicillin-susceptible *Staphylococcus aureus* infections have shown improved treatment outcomes in patients treated with β-lactams such as cefazolin in comparison to vancomycin, making this a specific area for potential antibiotic optimization.[45,46]
5. The diagnosis and management of peritonitis in PD patients are critical to reduce morbidity and mortality. The general practitioners might not be very familiar with the following facts[47]:
    1. A dialysis effluent white cell count > 100/μL (with 50% or greater neutrophils) is required for diagnosis, in addition to clinical features consistent with peritonitis (i.e., abdominal pain or cloudy dialysis effluent). This is compared to an absolute neutrophil count of 250 cells/μL or greater for the diagnosis of spontaneous bacterial peritonitis in cirrhotic individuals.
    2. Intraperitoneal administration of antibiotics is the preferred route unless there are features of systemic sepsis.
    3. Antifungal prophylaxis is warranted during the treatment of peritonitis in PD patients.

Limitations of the Study

Our study has a few limitations. The number of the survey respondents is relatively low (200 physicians) and a larger sample of respondents would provide more representative results. The survey did not include questions about medication use in ESKD like analgesics or antibiotics since that would make the survey longer and the response rate is expected to be lower. If medication management was included in the survey, we would have a better input about how general practitioners approach this important aspect in ESKD patients.

Availability of Data and Materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request

Ethics Committee Approval: The Luminis Health Clinical Research Committee has reviewed the protocol of this project and has determined that this research is Exempt under 45 CRF part 46.104, Category (iii). The request for waiver of HIPPA authorization has been approved.

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - E.E., E.A.; Design - E.E., E.A.; Supervision - E.A.; Materials - E.E.; Data Collection and/or Processing - E.E.; Analysis and/or Interpretation - E.E., E.A.; Literature Review - E.E., E.A.; Critical Review - E.E., E.A.

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responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. Government). Available at: https://www.usrds.org/media/2371/2019-executive-summary.pdf. Accessed 18 Oct 2020.
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