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Best Practices in Nutrition, Drug Management, and Multi-Organ Support in Patients with AKI

Announcer:
Welcome to this episode of KDIGO Conversations in Nephrology. This episode, titled Best Practices in Nutrition, Drug Management, and Multi-Organ Support in Patients with AKI, is provided by KDIGO and supported by an independent educational grant from Baxter. Here's your host, Dr. Marlies Ostermann.

Dr. Ostermann:
Hello, and welcome to KDIGO Conversations in Nephrology. I'm Marlies Ostermann. I'm a consultant in critical care and nephrology at Guy's and St Thomas' Hospital in London. And joining me today to discuss best practices in drug management, nutrition and multiorgan support is Professor Sandy Kane-Gill. It's a great honor to welcome Sandy. She's a Professor of Pharmacy and Therapeutics at the University of Pittsburgh School of Pharmacy, and she's also the current president of the Society of Critical Care Medicine, and an international expert in the management of patients with acute kidney injury, in particular management of drugs. Sandy, welcome to the program.

Dr. Kane-Gill:
Thank you, Marlies. Thank you very much for the opportunity to be here.

Dr. Ostermann:
So, Sandy, let's just start with a general question. Why do you think that critically ill patients are at risk for drug-induced acute kidney injury?

Dr. Kane-Gill:
Well, when you talk about why patients are at risk for drug-associated or drug-induced acute kidney injury, I think that primary reason comes back to the number of drugs that critically ill patients receive. Critically ill patients receive twice the number of drugs, as compared to non-critically ill patients, and this really increases their risk for adverse drug events overall and for drug-associated acute kidney injury. In fact, when you think about the drugs that they're receiving, about 20% of those drugs prescribed in the intensive care unit are considered to be nephrotoxic. So, you have these patients with very complex drug regimens, and then you quickly realize that the cumulative number of nephrotoxins that they're receiving can have this additive effect that's contributing to the stress on the kidney, and the result is acute kidney injury. Also, you know, Marlies, you asked me about drug-induced, and you can see I'm flipping back and forth between drug-induced and drug-associated, and so I think that's one of the important factors we need to think about. What are we calling these types of events? And maybe the drug-induced and drug-associated can be better differentiated. In these complex patients, it's difficult to isolate a drug cause, right? If the drug is the definitive cause, as opposed to something else that's going on with the patient? So, drug-associated acute kidney injury, or worsening of the existing acute kidney injury is also an important consideration, in addition to drug-induced. So, differentiating those is and can be important.

Dr. Ostermann:
Thank you, Sandy. Can you just clarify one thing for me? You mentioned drug-induced acute kidney injury. You mentioned drug-associated acute kidney injury, and earlier you said – you talked about nephrotoxicity. How do you describe these different terms?

Dr. Kane-Gill:
Yeah, I think drug-induced is when you have an event, and you can definitively say that the drug is the cause, so you're calling that a drug-induced event. When we think about drug-associated, you know, you have, again, this complex patient and they're developing acute kidney injury. Maybe it's due to their sepsis or maybe it's due to some other cause, and you have these drugs that can be

contributing to that as well. I think that's a drug-associated – it's associated with that AKI but it's maybe one factor amongst some other ones. And then, when we think about nephrotoxins you know, nephrotoxicity is an adverse drug event, and by definition, adverse drug event is harm associated with a medication. And that's very similar for nephrotoxins. It's damage or injury to the kidney from the drug.

Dr. Ostermann:
Quite complicated. But, you clearly outlined the various ways drugs can affect the kidneys. But sometimes, drugs are needed so in your experience, in your clinical experience and also when you teach colleagues, what do you say when nephrotoxic drugs are needed and, in particular in patients who are at risk of acute kidney? How should we manage them?

Dr. Kane-Gill:
Well, I think that management comes into thinking about, you know, when we think about nephrotoxicity, we say, okay, you know, our marker for that is typically serum creatinine, right? And so when you see a rise in serum creatinine, you think in about the drug, you think, okay, it could be drug-induced or drug-associated. Sometimes I think we first need to think about, while there's an increase in the serum creatinine, is it actually damage to the kidney? Because you can have a rise in serum creatinine associated with a drug that's not actually damage, so you know, it's important to remember that the serum creatinine can be affected by non-renal factors, such as age and gender and muscle mass and nutrition status and – also some renal factors that are independent of kidney function, such as drugs. So, for example, creatinine is both secreted and filtered, so it's possible that a drug can inhibit the secretion. I think this is a fundamental question that's going on in this debate, if piperacillin/ tazobactam plus vancomycin is really nephrotoxic, is it piperacillin/tazobactam can cause a reduction the tubular creatinine secretion because of the inhibition of an organic anion transporter.

And while we'll see that serum creatinine concentration rise with this –vancomycin/piperacillin/tazobactam, the drug combination may be injurious but maybe it's not. You know, at some point in time, we have this – just this uncertainty remains, and there's a continual data that evolving around this topic. So, you're asking me about management. I think one of the things we first need to think about is when we see that rise in serum creatinine is, is it really due to the drug? Is there some other factor going on? Is it really nephrotoxicity? And then you decide, okay, well, this looks to be associated with the drug, and it really is the nephrotoxin, and the serum creatinine could potentially be rising, so how do I manage that, or what do I do? In this case, what comes to mind immediately is nephrotoxin stewardship. It's really the strategic, coordinated effort to ensure kidney health by preventing acute kidney injury, or preventing worsening of CKD, or preventing the transition from AKI to CKD.

So, when you're talking about a situation where you need this nephrotoxic drug, I think hypervigilance is important, and surveillance is important, so even minor increases in serum creatinine can be considered and managed. I think it also goes back to what I mentioned earlier, which is thinking about the nephrotoxin administration. The presence of other nephrotoxins is important because what we think about in these complex drug regimens is this nephrotoxic burden and so the patient needs this nephrotoxin, but they're also receiving three other nephrotoxins. You know, does the patient really need all of them? Can we cut back on some of the nephrotoxins that they're receiving? And so management is about stewardship, management is about surveillance, and management is, in the cases of drugs, is also considering how many nephrotoxins they're receiving and do they need to receive all of those, and can we manage that better?

Dr. Ostermann:
Thank you very much, for this very clear summary. For those just tuning in, you're listening to KDIGO Conversations in Nephrology. Today's episode is on best practices in nutrition, drug management and multiorgan support in patients with acute kidney injury. I am Marlies Ostermann and I'm here with my friend and colleague, Professor Sandy Kane-Gill.

Sandy, we talked about prevention of acute kidney injury quite a bit, but occasionally, patients progress and need renal replacement therapy. How should clinicians manage medications in this cohort of patients with severe acute kidney injury, on organ support?

Dr. Kane-Gill:
Yeah. Well, drug removal is definitely influenced by the mode of the renal replacement therapy, that frequency of the dialysis, the flow rates of the renal replacement therapy. You know, just increased renal replacement therapy frequency can result in more drug removal. So, in general the slowest rate between the blood and the effluent rate is the one that ultimately determines solute clearance.

Now for example, when we're thinking about intermittent hemodialysis, the dialysate rate is usually twice that of the blood flow rate, and as such, the blood flow would determine the dialytic clearance. When we're thinking about how to dose a drug during RRT, we like to go back to our nice, traditional resources, potentially even the package inserts, which is supposed to be valuable with information, but the dosing recommendations that are provided for hemodialysis in package inserts are really not applicable to critically ill patients who are receiving intermittent hemodialysis, because the pharmacokinetic data were predominantly generated based on patients with end-stage renal disease.

I mentioned that drug removal is influenced by mode of renal replacement therapy, and frequency, so dosing would be different in

prolonged intermittent renal replacement therapy, compared to continuous renal replacement therapy. Now when we think about prolonged intermittent renal replacement therapy, it's usually operated about every 6-10 hours daily, and now we're giving a drug that is required to be given every 6-8 hours, and so sometimes it would need to be administered while – during a prolonged intermittent renal replacement therapy is operating, and so, this creates many questions. Do you administer the drug before? Do you administer the drug after? Or during the prolonged intermittent renal replacement therapy? Do you need to give a higher dose while prolonged intermittent renal replacement therapy is running, compared to when it's turned off? I have to say that even the experienced pharmacists have varying opinions about dosing, around prolonged intermittent renal replacement therapy, so as such, dosing varies widely, and standardization is really needed.

I wanted to mention continuous renal replacement therapy. When we think about continuous renal replacement therapy, we – you know, that's intended to be operated for 24 hours a day but I'm sure Marlies, as you very well know, that that doesn't always happen, right? That for some reason, that continuous renal replacement therapy is interrupted. And so, it's estimated that the clearance during CRRT is overestimated by about 24% to what's actually delivered, and so these overestimations can lead to potential drug accumulation with these interruptions. So, clinicians need to address drug dosing, according to when the CRRT is interrupted. Drug clearance can be calculated for CRRT, as long as you have a sieving coefficient and a saturation coefficient. Lots of things to consider here. You know, mode of RRT, frequency, when there's interruptions, so pretty complex in consideration.

Dr. Ostermann:
Sandy, could I just ask you – is drug accumulation the only danger during renal replacement therapy?

Dr. Kane-Gill:
Ah, good question. We are getting more and better data about underdosing, right? We're thinking about overdosing, and you're definitely getting to the concept of underdosing and that can be a consideration as well. And in fact, I think we're getting more data around doses that are needed, and maybe we're not dosing adequately. So underdosing is also a consideration. You also see us moving towards more discussions around therapeutic drug monitoring of antibiotics, to assure that we are in these target ranges for drug concentrations so that we're offering optimal therapy and, you know hopefully getting the best outcomes for patients as well.

Dr. Ostermann:
You've clearly outlined the complexity when patients need kidney replacement therapy. But in real life, in modern critical care, it can be even more complex. I'm just thinking of patients who not only need kidney replacement therapy, but also ECMO. Does this combination of multiorgan support affect drug dosing even more? Are there any particular considerations?

Dr. Kane-Gill:
Good question, Marlies. You're going way from the complicated to more complicated patients. ECMO and renal replacement therapy can both significantly alter the pharmacokinetics of medications, and generally, when we think about ECMO, or think about increases in volume of distribution, and it reduces drug clearance. But then, ECMO can also act as a reservoir that can be redistributing the drug back into the patient leading to some prolonged effects, especially for these lipophilic medications, such as propofol and fentanyl, midazolam – a sedative. So conversely, you can also have the ECMO membrane, and the tubing can adsorb some of the drugs and reduce plasma clearance, so we have this combination of things going on. And then, on top of that, we have the presence of the renal replacement therapy, and we just discussed that it has risk for both over and underdosing. So individualizing dosing regimens in patients receiving ECMO and RRT is really important. Therapeutic drug monitoring, when possible is going to help guide that therapy. These patients are just really complex, and in need of a comprehensive care with a multidisciplinary team, to offer these personalized patient considerations.

Dr. Ostermann:
Mmm. You – they clearly need the expert advice from expert pharmacists like you and your colleagues.

Dr. Kane-Gill:
Thanks. Yeah, it's a big effort, but it is complicated.

Dr. Ostermann:
As part of this conversation, we'd also like to briefly discuss nutrition, and in particular, in patients receiving renal support. Does the energy requirement differ for patients with acute kidney injury, who are treated with kidney replacement therapy?

Dr. Kane-Gill:
Yeah, really interesting that the – there's nutrition support guidelines for patients who have acute kidney injury that was just released by the Taiwan-AKI Task Force. And it addresses this exact question. The task force actually strongly supports a recommendation of 1B. So, strong recommendation, and with a reasonable amount of evidence to support the recommendation, that the energy requirement of

AKI with CRRT is the same as that for patients without dialysis. So, the energy expenditure of AKI patients is not affected by CRRT.

Dr. Ostermann:
That's very useful. Earlier, you outlined the fact that drugs get cleared during kidney replacement therapy. But so are water soluble vitamins, and nutrients. Therefore, in your role as a critical care pharmacist, do you advise the supplementation of micronutrients, to patients with acute kidney injury on renal replacement therapy?

Dr. Kane-Gill:
Yeah, that's another good question. You know, as you pointed out that, you know, we can think of clearance of these micronutrients quite similar to the clearance of drugs during something like CRRT, and we know that malnutrition is frequent in patients with AKI. So the nutrition clearance is – the nutrient clearance is potentially contributing to this complication of malnutrition, and you know, you highlighted that you know, there's clearance of low molecular weight and water soluble substances, such as glucose, amino acids, low molecular weight proteins, trace elements. So there's a risk for deficiencies in vitamin B1 and C and copper and selenium. So, the overall recommendation is that we should be monitoring these vitamins and amino acids especially during – for patients who are receiving prolonged renal replacement therapy. One of the reasons for doing this is just because these micronutrients have an essential role in immunologic and antioxidant functions, so, you know, these deficiencies could lead to poor outcomes in patients, and that can be concerning. We don't have any clear guidance on how to provide micronutrient supplementation and we do need some evidence around how to do this.

But it's, you know, the one recommendation we have is to make sure we're monitoring this and thinking about it as a contributing factor to why patient outcomes may not be what we're hoping them to be.

Dr. Ostermann:
Sandy, I'm afraid we're coming to the end of this discussion, but in our last few minutes, can you share with our audience some take-home messages?

Dr. Kane-Gill:
I think a take-home message is really about diligent, intentional, coordinated care for critically ill patients who have AKI and who have AKI requiring renal replacement therapy. And this really is down to an institutional commitment to nephrotoxin stewardship so that we can optimize patient outcomes. So really just thinking about how your institution can put this in place.

Dr. Ostermann:
Well, that's all we have time for today. I want to thank our audience for listening, and I want to thank you, Sandy, for joining me and for sharing all of your valuable insights. It was a pleasure speaking with you, and I learned a lot.

Dr. Kane-Gill:
Ah, the pleasure is all mine, Dr. Ostermann. Thank you for having me.

Dr. Ostermann:
I'm Marlies Ostermann. To access this and other episodes in our series, visit KDIGO on Spotify, or kdigo.org/podcasts. Thank you for listening.