Andy Lewington, MD
Therapeutic Challenges in AKI and CKD:
Managing Hypo and Hyperkalemia

Qi Qian, MD
Hypernatremia - Pathophysiology and treatment: Case-based discussion

Speaker 1 (00:00:00):
Good morning everybody. We are honored to have two wonderful speakers this morning with the topic dysnatremia from hyponatremia and then ending with hypernatremia. Our goal is to make the session as interactive as possible, so please feel free to stop us for questions and try to make it more interactive and more interesting. The first speaker is, Dr Andy Lewington. I have had the pleasure to know Andy for a while, he has done significant amount of work for betterment of our patients, their patients in Leeds a UK AKI management. He has extensive experience in management of hyponatraemia, he's associate professor, clinical professor in Leeds and he's going to enlighten us with the topic of hyponatraemia.

Speaker 2 (00:01:01):
Thank you very much for that lovely welcome. I'm blessed today that I do have, an expert with me in dystrophemia to see you over there so I can look to her and I'm sure there's a number of you in the audience that, perhaps when I look around more than I do about this, I've heard you speak over the years. So, I'm going to talk about hyponatraemia and sorry, that's the way we spell it in the UK. I did train in the U S for 4 years as a fellow. So I did spell it the other way for a while. In fact, I probably learned most about it when I was over there. Because even in the States you certainly do spend much more time looking at the acid base in the physiology than we do in the UK.

New Speaker (00:01:40):
it was something I was quite fascinated by when I went back to the UK having spent lots of time looking at cases and looking into Burton Rose's book on elyctrolytes those are fond memories of those years. But now I'm in Leeds and that's in the North of England where that little red is, we're in Yorkshire. And, we've got some lovely countryside there and two big

hospitals that I work in. So, a few disclosures of interest, to start off with, I'm going to give a bit of an outline on the physiology, not in great detail. I spend quite a lot of time, so immersing myself back into this subject and it does get quite complicated actually. So I'll try to do it as, simple as possible probably for me to understand this. Because I think one of the indications that you understand something is that you can teach them it.

Speaker 2 (00:02:31):

So you can judge me from that. I'm gonna look at the causes, the complications clinical assessment, treatment, and the case presentation. So physiology sodium is the extracellular ion, normal, greater than135. That's a debatable as to where you are. But in my hospital, it's great than 135 is normal and it's responsible for osmolality. People do talk about tonicity and I didn't really want to get too much into honesty versus osmolality. I don't think that's appropriate necessity for this talk it's an exracellular ion and it's responsible for the osmolality. And we can see the equation there, the classic equation that gives you the osmolality. you can put in the blood urea nitrogen, the glucose values and calculate it. So what is osmolality? I think there's a lot of confusion as to osmolality osmolarity.

Speaker 2 (00:03:19):

Osmolality is a total number of moles of solute per kilogram of a solvent, and it runs in our hospital between 275 and 290. Definitions, it depends, 280 to 290. So it depends where you are, in the world as to what your range will be. And it determines the chancellor distribution of water. the concentration, is a sodium concentration and osmolality is maintained by urinary excretion of sodium and water. And this is fine tuned by the ADH secretion affecting the convoluted tubule in terms of the concentration that occurs of the urine. The final pass of what happens to the urine as it makes its way through, the kidney and allows you to excrete, large amounts of dilute urine as necessary. And this is supported by the countercurrent mechanism that's set up in the kidney.

Speaker 2 (00:04:15):

So the maximum daily urine output can be up to about 10 liters. The minimum urine osmolality is around 50 to a 100 milliosmoles per kilogram and the maximum urine osmolality and Qi updated me on this is really age based but can be up to a thousand milliosmoles per kilogram. The symptoms of a patient who develops, hyponatremia, will depended on the

severity and the rate of the sodium reduction. Gradual decrease in sodium usually results in minimal symptoms. I'm sure we see a number of our patients have minimal, decreases in sodium. So now I see a number of patients in my clinics that, the sodium transiently goes into the red zone and then comes back out again, rapid decreases can result in severe symptoms of cerebral oedema. So polydypsia, muscle cramps, headaches, confusion, altered mental status, coma and status epilepticus.

Speaker 2 (00:05:08):

So it's a dangerous thing that can happen and must not be underestimated. The causes, people divide this into different ways of looking at it. And I've just done the traditional way that I've learned about it, which holds good for me. But you may go away or you may have a different way of classifying it, but you've got pseudohyponatremia which may be hyperlipidemia, hyperglycemia underlying it, or a case of myeloma with hyperproteinemia underlying this. So again, look for the cause. You see something, you look for the cause of that hypovolaemic, hyponatremia, diuretics, GI losses, adrenal insufficiency. osmotic diuresis, salt wasting nephropathies. There's a group there of causes. Then there's hypervolaemic hyponatraemia. This does somewhat depend on your skills in terms of examining the patient, determine their volume status. And that makes this classification a little bit harder to be sure upon.

Speaker 2 (00:06:00):

but we've got heart failure where there's reduced cardiac output and unsuppressed ADH, liver cirrhosis where there's arterial vasodilatation on the unsuppressed ADH.and then we've got chronic kidney disease. And, this is where you've got an eGFR, which is less than around 15, where the kidney just cannot, dilute the urine any lower than 200, 250 milliosmoles per kilogram. And this got me thinking the other day that I see quite a few of my patients. I do a lot of work with kidney transplantation. We have over a thousand kidney transplants I look after in clinics and do over 200 kidney transplants a year. And a number of my patients postoperatively, their kidneys are not functioning to start with are in delay graph function. They become hyponatraemic. And I suspect it's, for this reason there just aren't enough functioning tubals there to maximally remove as much water as necessary.

Speaker 2 (00:06:49):

So it's something that I'm going to take a keen look at and try and understand when I go back and probably measure their osmolality just to see if this is what's going on in that group of patients. Then there's euvolaemic hyponatremia with malnourishment. it can happen with exercise and.Mitchell Rosner around the next door somewhere. He's, one of the true experts on hyponatremia I would say. And I've sat in his talks over the years when I've come here and he talks about the marathon runners and the risks of hyponatraemia in those patients. That can be a lot of consumption of just, hypotonic fluids. And then at the end, the sudden ingestion or absorption of the water at the end of the run can result in that sodium dropping at the end and resulting particularly in women.

Speaker 2 (00:07:29):

A high risk situation, prostate surgery, polydypsia, with the prostate surgery, Sorbitol irrigation absorption of this particular fluid that doesn't contain any sodium and then syndrome of inappropriate antidiuretic hormone. And, there's no real causes of this, CNS disease, malignancy drugs, fluoxetine, hypothyroidism, adrenal insufficiency, pulmonary disease, recent surgery. And, I think it's seen happen in more cases than we can imagine. certainly I think a syndrome inappropriate IDH is going on quite a lot around us to a certain extent. I used to think of is very defined entity, but I think there's different levels of it. Clinical assessment involves, the comprehensive clinical evaluation on the mental status. You know, are they actually now at risk? Are they becoming so confused? It's now an urgent situation. Identify those potential causes. They had recent surgery medications. So your history tries to identify one of the causes I've talked about already.

Speaker 2 (00:08:24):

volume status, hypovolaemic euvolaemic hypervolaemic. So have a look at that to determine the volume status of the patient and some basic investigations to perform, which enable them to work through, an algorithm of what's actually causing the hyponatremia in this patient. You don't have to do urine sodium in all patients, but you will be triggered at a certain point. So here we see a potential assessment of hypernatraemia got this from the American Family Physician of 2015. And this looks at patients with their sodium that are low. Here it says less than 135, and then it looks across here and determines, whether these patients that were first of all looks at their, serum osmolality, are they asymptomatic? Are they symptomatic?

They're symptomatic and you go straight down to an urgent pathway of treatment. If they're asymptomatic, you've got a bit more time.

New Speaker (00:09:14):
so determine their sodium, osmolality is it normal? Is it low or is it high? and this will affect the decision making process. If it's normal, that's 280 to 285, then that may well be that you assessed that perhaps they have hyperlipidemia as a cause or a pseudohyponatremia. If it's high, then you may want to consider that may be, something such as, hypoglycemia causing it. And then we've got the one that leads to the most, commonly seen is where there's a low osmolality where this is less than 280. and then you'll move on to assess this patient in terms of the potential causes. If urine osmolality has less than a hundred, then you'll consider that it's a psychogenic polydipsia of the urine osmolality is greater than a 100.

New Speaker (00:10:05):
then you'll be assessing the kidney function in that patient. And again, this is when you examine the patient. You've already examined it at this stage, whether euvolaemic, hypervolaemic or hypovolaemic. And then you will start looking at the urinary sodium to determine what you actually think the cause might be. So it starts to break down quite nicely if you follow this sort of algorithm. So in terms of the treatment, what are the key considerations? I think it's the duration of the hyponatremia. It's acute less than 48 hours. Then you can try and recreate that quickly. If it's chronic, more than 48 hours, you've got the situation where the intracellular state has changed and you've got the development of these osmolytes which are trying to counteract the movement of water and what will happen then if you try and correct too quickly, then you're at certainly risk the water moving too quickly out of the cells and leading to severe brain injury.

Speaker 2 (00:10:54):
The severity is important. So in terms of the rate of correction of sodium, people would consider severe hyponatremia is a sodium less than 120 with neurological symptoms. Again, it can vary at different levels. You see the case that I present in a minute, you'll see that the urological symptoms weren't very severe at all. A rapid initial correction is advocated in these patients where a severe neurological symptoms that are occurring 4 to 6 milliequivalents in the first 4 to 6 hours, of course, identify what the cause is, what's underlying it. And generally speaking, try and avoid correcting the

sodium by more than eight milliequivalents per liter in at 24 hour period. If the duration of the hyponatremia is greater than 48 hours. And in fact, I have seen a patient, sadly where the correction was within that range but still developed the severe consequences of the corrections.

Speaker 2 (00:11:48):

So I think you have to be very cautious here that there's a push to correct it rapidly, but then just ease back a bit because, there are severe consequences to this in terms of osmotic demyelination occurring. So in terms of the treatment of the, severe cases, people advocate using 3% saline, I've never done that myself personally or had to, I probably just haven't seen enough cases, I'm sure there may be some people in the audience that had to use 3% saline and they see a few people nodding their heads. So you can use one or two of these different combinations to do that. Trying to bring up the sodium. Again, the principle is to bring it up quickly to start with, but then slow that down, temporize it. And some people talk about using, desmopressin also to use that at the same time, just to be careful that you don't suddenly get a loss or, over rapid correction occurring.

Speaker 2 (00:12:41):

Again. I don't people have done, they use desmopressin at the same time as giving the saline , again few people are nodding. So, these are things that people are practicing. So what's the risk of overly rapid correction is osmotic demyelination this does occur classically a few days afterwards. You think you've improved things, but then the patient starts to be unwell. And this results in the rapid movement of the water out of the cells I described before, the patient can suffer from seizures, disturbed consciousness and suffering gait changes. And this can be seen on MRI changes. And this is what I just picked up from this journal example. And you can see here, there's changes here. The signal is intensified in the basal ganglia regions. So it's best picked up by an MRI if you're suspecting it in terms of mild to moderate type hyponatraemia, where the levels of sodium, maybe 120 to 129.

Speaker 2 (00:13:32):

Again, I think it depends on clinical context. Then with those less severe symptoms, symptoms identify any reversible causes. So there may well be things that you can do to start with stop a drug, in that particular patient,

reduce the amount of fluid that they're drinking and advocate perhaps the use of oral salts and 9 grams of oral equals around 154 milliequivalents of sodium such as you would see in a bag of normal saline. What about Tolvaptan an ADH antagonist? We only use that at the moment in the UK for a also more dominant polycystic kidney disease. And I know we've had to set up specialized clinics for these, because Tolvaptan can have quite severe side effects, it can lead to very rapid dehydration in a patient and hepato-toxicity is another potential side effect.

Speaker 2 (00:14:22):

So we have to have a whole team involved with these patients when we use it because they're using it for a period of time monitor liver function tests, so on. So, I haven't gotten any experience of using inpatients with SIDH, but colleagues May and Qi kindly offered to talk about that more of necessarily get some questions and answers about the way you might want to use that if necessary. But it is out there. What about renal replacement therapy? certainly the patient has an acute onset of the hyponatremia less than 48 hours. Then these are the sort of classic cases where I'd be involved in the setting of acute kidney injury where there's a volume overload in that patient and there's not a lot of room , to manipulate things. The patient's oliguric and, you're getting into difficulty here in terms of trying to do those other things.

Speaker 2 (00:15:10):

We talked about the medical management. So, I think in these cases, I'm happy to put the patient on dialysis and rapidly correct, the sodium if this happened over a short period of time.And then you can use intermittent hemodialysis if that's what you have, where you are or you can use, continuous therapy if necessary, that will correct things fairly quickly. I found certainly in terms of using continuous veno-venous hemodialysis as we use in Leeds with citrate anticoagulation. What about patients who've got the chronic onset greater than 48 hours? Well, again, the same setting these patients where there's not a lot of room to maneuver in terms of trying to, restrict their fluids or maybe try and manipulate other things, gradual correction is recommended and what I've classically done is put people onto CRRT and just measured as we've gone through the sodium, as we, treat the patient and weigh things up as to whether we slow things down or we can take them through for a longer course, but essentially just do that with the treatment.

Speaker 2 (00:16:14):

I can't change, the sodium baths and the patients that in terms of the treatment modality that I have to hand, I don't know. People can do that in their own institutions or they can make those manipulations, but certainly I can't do that. And is there something we can do in the UK? People do talk about doing that.

Speaker 2 (00:16:33):

Right. So giving you the background to sodium, some physiology talked about how you might investigate it. So I'm going to now present, a patient that, we looked after not so long ago, this was a 65 year old male who has end stage kidney disease secondary to membranous glomerulonephritis and he had a kidney transplant back in 2006. Pseudonymized this, change, some of the things, this was, a real case biventricular heart failure and had bronchiectasis. He was admitted back in November of 2017 and he'd felt generally unwell for a month of lethargy, reduced appetite. His weight was 52 kgs. He'd had fevers increasing breathless for the last three months and reduced exercise tolerance

Speaker 2 (00:17:19):

so he was on his standard immunosuppression or we used tacrolimus and mycophenolate mofetil and our patients who was on paracetamol and fluoxetine. You might recognize fluoxetine as one of the drugs I've already alluded to that can be associated with patients who develop hyponatremia, lansoprazole, atorvastatin statin, ramipril and furosemide So a standard fare of drugs that we would use in the patients who had very small list of drugs compared to the list of drugs most of our patients have. On examination, he was alert, he wasn't confused at all. He wasn't feeling well and maybe there was a subtlety there the manifestation of the hypornatremia, but he was, aware of what was happening and he was normovolemic on examination may be little bit dry blood pressure is 80 over 50, his crackles at his lung bases.

Speaker 2 (00:18:06):

oxygen saturations were 95%. We weren't really able to exercise test him because he was quite unwell and we brought him in. Investigations demonstrate Dhe had hypernatremia, hypercalcemia and an elevated CRP, C- reactive protein. So you can see those. I think they project quite well up there. We can see that the sodium on admission was 117 and this

individual, the sodium had been down for a little while. It'd been drifting its way down, but I think we just ignored that in the clinic. we have some patients where it does seem to reset or the lower value, but then it really truly starts to drop much lower here. And if we look across here, we can also see, that he's not particularly well nourished at the moment. His albumin dropped down to 34 having been in the normal range and his adjusted calcium is up at 2.94, normal will be up to 2.6, in the UK. His creatinine was 102 and his full blood count, he was anemic. His platelets are on the higher side.

Speaker 2 (00:19:12):

His glucose came back as 6.6. Okay. So a normal range there is on the side of the reference range is 3.56, so it wasn't hyporglycemic, PTH was 6. So that wasn't a maximally suppressed really for somebody with such a high calcium. That's something to think about for the future. And that was his chest x-ray. So he's got this interstitial shadowing across, here, and, he's got some signs of the bronchiectasis in the lower lung zones. So perihilar interstitial oedema was reported by the radiologist. So he came in, he had some fluid resuscitation with 0.9 sodium chloride. That was for the fluid resuscitation, not to really try and, treat the hypornatremia.

Speaker 2 (00:20:04):

You wouldn't really use 0.9% sodium chloride to do that and that's not something you would use as a standard treatment. tTe patient also had oral fluid restriction. The fluoxetine was stopped, had to have some pamidronate to treat the hypercalcemia. And then there was some dietitian input because this man was quite severely malnourished now . We got the, electrophoresis back and that was O.K So again, just making sure they're not other causes for pseudo hypernatremia. We sent off the other investigations, but waiting for those to come back. You can see the patient truly had a Hypo-osmolar hyponatremia with an osmolality of 251 normal being 275 to 295. So it truly was a case of hypo-osmolar hyponatremia that we were dealing with. Urine osmolality came back at 146. So that strikes me that he's not able to maximally dilute his urine down.

Speaker 2 (00:21:07):

Is that because he's got a bit of kidney impairment? his eGFR I was around 65, I think. or is it because there's some syndrome even in procreation, ADH flying around the system? urine sodium comes back as a 28, so not

less than 20 and it doesn't really help us too much, I would say there. And then we went on and performed a CT because he had these respiratory symptoms and, the CT scan, here demonstrated that he had extensive groundglass type inflammatory changes predominantly in the upper lobes. So this is an immunosuppressed patient, with these CT findings. So we were getting quite worried at now. So we asked the respiratory team to come along and help and he had a bronchoscopy and that showed abnormal left lower lobe with extensive secretions in that lobe. So, we did a number of tests that started to come back. The CV was just only mildly elevated, wouldn't be too excited about that sort of level of CMV in the blood.

Speaker 2 (00:22:06):

AAFB microscopy was performed, it wasn't seen and then subsequently came back as negative eight weeks later. And then this came back, a phone call at 4:40 PM. The further results from the BAL, a high load of PCP. So, this patient, we got a diagnosis here, so he's got pneumocystis carinii and he was, allergic to trimethoprim and therefore was commenced on primaquine, and clindamycin for 21 days to treat his PCP. We can see that over the course of time is, after we started treatment, we started creating other things his sodium does gradually start to come back up nicely, his creatinine value is eGFRs are holding here at around 62. We can see here his CRP starts to rise, so he starts to develop, some infection whilst he's in the hospital with some further, or this is his PCP before we actually got him on treatment that's getting worse and his calcium has remained high throughout this, admission. We have treated him with mofetil from a few occasions now. So there we can see the sodium starting to rise nicely and the setting of the CRP that was getting worse related to his pneumocystis.

Speaker 2 (00:23:26):

So he was finally discharged and we can see that things did correct as sodium came up to 133. his eGFR is around 65 his calcium had normalized and a little bit there a little bit higher on that occasion. So in summary of this case, it was a patient who had chronic hypo-osmolar hyponatremia I think you'll see how we use the, the algorithms, the tests, to work our way through this , to determine it. the patient did appear to be euvolemic when they were admitted. there are probably multiple causes in this patient and I think that's the thing to look out for in your patients that there's often multiple causes to these episodes of hyponatremia, he was malnourished.

He didn't have as much protein intake he had Fluoxetine and had the diagnosis of PCP, so had lung disease and lung diseases that cause a syndrome, inappropriate ADH.

Speaker 2 (00:24:17):

I think all these factors came together in this individual, to present in the way he did. But he was having a lower sodium for quite some time before we admitted him. And his urine osmolality was not maximally, diluted. It was 146. I think there was, some syndrome, inappropriate ADH going on in this individual patient. So I in conclusions on hypenatremia certainly as as me as a clinician, I'm a full time and HS coalition. That's a what I specialize in is looking after to patients and responding to consults and going to seeing them is that you need a comprehensive clinical evaluation on your patient. You need to take into account many different possible causes. You want to understand the duration of the episode. You want to understand the severity. You want to consider that in terms of how quickly you need to treat the patient.

Speaker 2 (00:25:06):

You then trigger your investigations, you're looking for the cause and then the treatment. You've just got to temporize things here because the knee jerk is to try and get the sodium up, as quick as you can. But you've just got to be aware that the consequences of doing it too rapidly can be severe. And as I said, I have seen a patient that suffered the consequences of this despite trying to bring it up very cautiously in that individual. And the consequence of treatment can be worse than actually the consequences of the hyponatraemia in patients who have had chronically. So I just like to thank you for your time and happy to fill any questions as Kanish wants us ,how you want to do Kanish , comment about the case or presentation.

Speaker 4 (00:25:51):

So can I ask you to stand by? So I want to come back to the case and I can make some other comments. But, first of all, he comes in hypotensive on a diuretic and perhaps not doing well for a month. So I don't believe that we're great at assessing clinically volume. So there's a possibility that he's actually volume depleted. That's number one. Number two, when did you do the urine electrolytes relative to his last dose of furosemide?

Speaker 2 (00:26:34):

Did I say he was on furosemide, Might've I left furosemide on there? Oh no, he wasn't on furosemide That's not meant to be on that slide. So he wasn't on a diuretic. I think he was relatively hypotensive. I think he was in a septic state. So I think, it was hard to assess his volume. I admitted him from clinic, but he had no overt edema, but his blood pressure was saggy. Well, I take your point, but he didn't, he wasn't on a loop diuretic. I went through and check that. And that shouldn't have been on the slide. Apologies for that. That's a classic.

Speaker 4 (00:27:08):

So the other things that we pay attention to when we look at urine electrolytes is they help us determine whether someone will respond to just restricting volume. And so the madias kind of approach of, looking at the sum of sodium, assim in the urine, if it's close to the serum sodium, they're not going to respond to just restricting volume. So that helps us. And the other is the osmolality. So, you know, if you've got an osmolality that's greater than serum osmolality,, usually they don't even respond to normal saline. You need, to give something that's hypertonic to whatever their urine is. So those are additional reasons, to do urines and to get that information. Even if you think you know, what the diagnosis is.

Speaker 2 (00:28:10):

No, thank you. There are very good points, in terms of the use of diuretic that would cause a loss of sodium in the urine and would confound any tests. So you need to bear that in mind. but he wasn't on the loop. [inaudible] he didn't require a new director. His function was good enough. His kidney function was as such didn't require a diuretic.

Speaker 4 (00:28:30):

Would you introduce yourself before hand? Ali Basheer with the faculty at the University of Nebraska. Thank you for the talk and the case. and I'm at a loss to see how things work in UK. However, majority of the times when we come into play, these patients who are usually hypovolemic diarrhetic or some other cause or hypovolaemiae form of intercurrent illness complicating underlying hyponatremia from some other reason, they are already polyuric and they're all correcting. And we've tried to go around and teach the ER physicians. we end up using desmopressin quite a bit because when we come into play 4 or 5, 6 hours, if patients are already or

in or they are 8.9 point rise, how often do you use desmopressin and are there any guidelines in UK?

Speaker 2 (00:29:35):
So as I said, I really haven't used, desmopressin so if there's not something I'm getting called in the U K to go and see. So it makes me wonder, so you see a number of these cases where usually in the ER rooms or across the hospital and anywhere in particular where this is happening. So the ER physicians usually will,

New Speaker (00:29:55):
treat them. And then a lot of times these specialists are not hypotensive. So hyponatremia is treated a normal saline isotonic saline, so sort of try to go around the other, I think Rich Sterns i had a paper out 2 years ago where they looked at series of cases where they would treat them upfront with desmopressin and hypertonic saline as a safe way of bringing the sodium up in a controlled fashion. So I just was curious to know if in Europe, in terms of the use of desmopressin.

Speaker 2 (00:30:33):
We're not really using it an I think Leeds would be reflective of practice across, we are one of the largest NHS trust in the country. So, I would know about if we were using it because they wouldn't use it without asking us. So we're just not using it like it's used in the States. But I think I'll go back to look at the speech of the biochemist and find out whether we're getting, some hyponatremic cases that are going on in, in our ED as we call them, emergency departments and try and understand why we don't see that phenomenon as commonly as you're seeing it. Also ask the pharmacist whether people are prescribing desmopressin because I'm not aware of it at all.

Speaker 1 (00:31:08):
So thank you. Obviously see different practices. Thank you for the question. I have a question or discussion for the audience. So, as Doctor Lewington mentioned patient was malnourished and hypotensive, how many of you would give these patients more osom in a form of 3% sailne? Raise of hand please. Why don't you give normal saline I agree with you. I wouldn't use normal saline but why? Can you go back to history?

New Speaker (00:31:44):
Can I go back on this or do you have to do it for me?

Speaker 1 (00:31:48):
So yeah, the history of biventricular heart failure, so 3% saline may not be indicated, one of the options that Dr. Lewington mentioned is therapeutic options and the treatment plans was probably kind of playing a big role, in his recovery. And that was dietition consult how many of you would give these patients more osom in the form of protein or urea? Can you comment on, impact of osmolar intake in hyponatremia? So we have access to urea, we use it very often among patients, particularly malnourished patients. It gives these patients enough osom to be able to excrete extra water. obviously before having access to urea used to put these patients about 2 grams or two and a half per kg per day of protein for 24, 48 hours. These are patients that really need additional osoms to be able to excrete extra water.

New Speaker (00:32:53):
As you know, in American diets, we usually generate and take about 6 to 900 miliosom per day. And if we dilute our urine to the maximum of 60 milliosom in per liter, then we can drink 10 liters of water to treat 600 miliasom per day but, if we drink 11 liters, then that extra liter stays in us and causes hyponatremia among patients with malnutrition, they do not generate or take 600 miliosom per day. They take about 200 miliosom per day or even less. So those patients, instead of 10 liters being safe for them, about three to four liters is safe. And if they take a little more, they become hyponatremic giving them more osom allows them to excrete extra additional volume of free water and therefore correct their hyponatremia. We use these a additional osom intake, particularly for ICU patients rather, very often it is safe medication.

Speaker 1 (00:33:55):
It doesn't cause uremia it is normally thought, doesn't correct sodium really quickly. we have had very good experience. We start from 15 and it's very non-expensive., we start from 15 gram twice a day. It comes in the form of packet. It smells really not nicely. We mix it with juice a little bit, and you can increase it to 30 gram bid and over the course of 18 to 24 hours, you'll see that sodium start going up slowly. If you don't have access to urea certainly taking additional protein for malnourished patient would help.

Speaker 2 (00:34:37):
Yeah, that's, show the next point of malnourishment was a big feature in this. This man, his protein intake was very low. His weight, as you could see was 52. So, he was really struggling and his ability therefore to, concentrated urine was as much reduced.

Speaker 1 (00:34:55):
How many would use Lasix?

Speaker 6 (00:35:06):
We tried to get ure-Na in our hospital formulary. It's not a drug it's a dietary suplement , that is correct going back and forth as had the right in our institution to actually, okay. we used to prescribe ure-Na.

Speaker 1 (00:35:34):
So we were contacted by pharmacies. It's kind of the way they work in our institution that this is available and this is the paper CJASN, this was published about six months ago that showed efficacy of using urea in patients with hyponatremia. And we had a very kind of big conversation. I actually voted no for urea, but everybody else did voted yes. Now that I'm using it, I really kind of think that this is really the revolutionary on patients that are very malnourished. It helps them to correct their sodium very safely.

Speaker 6 (00:36:09):
[inaudible] lox was in the hospital, you know,

Speaker 1 (00:36:23):
as it is food supplement. I tried one of the packets myself. It is absolutely not edible or palatable. You really need to want your sodium to be corrected to kind of be able to take it. So in ICU we have the luxury that patients do not have many choices. We give them the medication through the g-tube or w give them the medication they have to take it and nurses are like hawks on the top of their head. But I agree with you that taking urea in a long term may not be feasible. However those patients we can make sure that they follow with our nutritionist in order to take additional protein. As you know, each 10 gram of protein would be converted to about 50 millimole of urea and that would potentially kind of become very close to what they need. And it's a lot more delicious than urea.

Speaker 8 (00:37:16):

I usually ask them to take an extra protein shake so they can pick the chocolate color flavor, vanilla flavor. If you have two three units of protein shake that corrects quite a bit.

Speaker 2 (00:37:36):

Can I just ask you if anyone seen osmotic demyelination Are they seen that occurrence? And was it because it was corrected too quickly or were they just very sensitive patients for other reasons? high risk,

Speaker 1 (00:37:53):

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Speaker 2 (00:37:55):

I'm Greg Brown. I'm an intensivist, with the military in Germany, yeah, I've seen it a couple of times, but primarily, where I've seen it very often as an alcoholic patients. And it kind of asks the question, do they actually do this themselves and do they actually come in with this phenomenon? Because oftentimes just, through bridge binge drinking episodes, you know, just, just massive osmotic shifts between periods of when they're not taking in a lot of alcohol and then when they are, and then obviously malnourished because essentially they're drinking their breakfast but, I remember taking care of one particular patient were

Speaker 5 (00:38:37):

I actually was trying to drive their sodium in the setting of a alcoholic hepatitis, because I was concerned, for cerebral edema if there is ammonia being so high and, in doing so, I mean I was very careful and I tried to make sure to be very slow to bring his sodium up and subsequently, when you just start coming around, in terms of his mental status, he had a lot of lemia ataxia you and when we send out the MRI, he had evidence of a osmotic demyelination. And, I was sitting there probably for a good part of the hour, self widelating what I'd done wrong, but also, just kind of going over and over again with numbers. And one of my nephrology colleague called me and says, Greg, it's okay. You did not do this. I want over the numbers myself and this is unfortunately, this is what we see. So thank you for sharing that.

Speaker 8 (00:39:33):

Could I just commnet on that for the patient, chronically malnourished liver disease, a woman, and, they are very sensitive for the myelination and malnourished patient that you need to correct extra, extra slowly because they don't have enough osom to go around together, so sometimes, in our experience as I go much slower with the liver failure, malnourished patient

Speaker 1 (00:40:23):

we always say this is not the target. This is the ceiling, right? So you, you want to avoid more than six, but it doesn't mean that you need to actually achieve six this lower you improve sodium after recovery from symptoms and signs of hyponatremia, the better it is. So we kind of rather go very slowly. So, as time is a over, thank you Dr Lewington,

Qi Qian **Hypernatremia**: Pathophysiology and treatment :Case-based discussion

New Speaker (00:40:47):

I would like to introduce the next speaker, professor, Qi Qian we call her encyclopedia as she is based in our clinic, her office is couple of doors down from my office she's director of acid-based electrolyte group in our institution, she has given many talks, around the globe about acid based electrolyte disorders and she's a full professor in medicine and physiology.

Speaker 8 (00:41:19):

Thank you so much Kanash for the overly generous introduction. So, my task today is talk about hypernatraemia. It's different, You have to remember, hypo is not symmetrical process. And we want to talk about what's the optimal consentratoin of sodium. very briefly, pathophysiology and treatment. Do's and don't s. I went to discuss two cases first one is 79 year old woman nursing home resident hypertension. previously had a stroke, came in with worsening mental status over the last five days. And the evaluation revealed that she was a somnolent. She's febrile, chest x-ray showed pneumonia laboratory study, sodium was 170. And first thing you always want to look at is if you could get a urine sample to take a look at the urine osmolality. And in her case, urine concentrated 780. And she got one liter of isotonic, saline en route.

New Speaker (00:42:37):

she has SMA, Amanda, Yara and output. so, you're dealing with this kind of situation, acute fabry illness, over the course of last five days. And second case is 35 year old woman, bipolar disorder, past suicide attempts, presented. There was bed wetting, essentially lots of nocturia and she was started on lithium and that's the last resort beause she tried many other agents and didn't work and she was on it for the past seven months and she's bothered by nocturia. recently she had a fasting serum sodium was 147 and, 24- hour urine volume with 5.7 liters and urine osmolality is 160. So that's the two case. So in order to develop hypernatremia, you have to have these two conditions. One is total body, water deficiency, either absolute or relative. And the exchangeable sodium had to go up sometimes.

Speaker 8 (00:43:57):

So when the potassium is low, you give potassium, you could further raise sodium. So in order to save the water, kidney is a major organ. So there's a two major regulators for urine concentration, one is AVP we know very well. Another tonicity elongated enhaner binding protein (TonEBone) is transcription factor and you need both factors. They are now redundant and synergistic. AVP. we know very well. It's a stimulate transcription translation, epico insertion, of aquaporin 2. but tonicity elongation, binding protein, senses the high, osmolality pressure and the producers these osmolites so that the tubular cells could survive in that kind of a concentrated, environment. How do we know that is because when you knock down the tonicity elongation and binding protein also called NFAT5 most of the mice cannot survive for the mice who a few mice survived.

Speaker 8 (00:45:21):

They don't have these osmolites. And if you're looking at the kidneys, there is no medullary regions, despite they have perfectly normal AVP and they cannot concentrate urine, they have a high sodium concentration. So it's become very clear. You need both AVP and you also need a tonicity like a binding protein. So the next factor, that could be run is the exchangeable sodium. In the past we always saying exchangeable sodium is controlled by, you have an input then the kidneys start to regulate it take a while for the kidney to unload the sodium. And that's the two compartment, a situation where the most famous, calculating formulas, derived from. But in the last decade, we also, started to get to know the tissue storage of sodium. For instance. this is a slide of an elderly man who is laid up with

sodium as versus a normal young man who has a very little sodium, mostly in the muscle and in the skin.

Speaker 8 (00:46:49):

And turns out there is a school of evidence showing that these tissues sodium could go in and out, from a osmotically active situation to goes into the, tissue become as osmatically inactive and sometimes it's comes out to through lymphatic regulations. These in itself, could be a kind of a talk about so just to remember, tissue storage, poor sodium sometimes contribute to the sodium homeostasis. this is a very interesting study. this is a group of a normal, adults and receive no amount of salt . And then they look at their urine sodium excretion. And you can see if you use very two well known, formula to predict their sodium excretion is this number, but in reality, are these normal people who has a normal kidney regulatory function? They are excreting sodium, very different from what the, formula could, predict.

Speaker 8 (00:48:14):

So what I would say is that maybe the tissue storage of sodium contributing in and out from osmo active to osmo inactive vice versa, contribute to these imprecisenes But I think at the most important point for our practitioner is we cannot rely on the formula to guide our, fluids provision. So what is the best sodium concentration in the blood? there's a number of studies including recently we look at the Mayo data and it's become very clear. The best, sodium concentrations are somewhere 140 plus minus 2. That's typically associated with a very low mortality rate. And then beyond that, you started to have high mortality. and ,interestingly in the last two decades, for instance, the occurrence of a hyperkalemia, but can this in the past was this amount and the occurrence of a hyperkalemia in critical care patients have become over doubled, in the last two decades.

Speaker 8 (00:49:31):

More importantly, if you're looking at the mortality associated with hypernatremia almost more than double. then the mortality rate of a hyponatremia, even with very mild hypernatremia less than 150. If you don't correct it, they have a 28 day mortality could be more than 20%. So it's much more deadly situation than hyponetremia This is a relatively large mulicenter study. critically ill patients, if you're looking at the, borderline hypernatremia, a short term mortality, this is a 28 day mortality, 22%, 32%

39% 54% these are after you adjust everything under the sun, it's still independent contributor of a mortality.

Speaker 8 (00:50:34):
When you look at the patient with hypernatremia, there's a laundry list of the stuff that you have to check out to make sure these are not play into, the situation that caused hypernatremia. But most typical scenario would be the DI sometimes clear cut, sometimes not clear cut, insensible loss usually coupled with, pyrexia for instance, our first case is the fever, insensible loss. An you could have a hypotonic sodium lasts like a GI. so the osmotic diuresis and the one very common occurrence is hospital acquired. Hospital, acquired especially in critical care patients, that become more and more common. Actually, it's worse mortality compared to the community acquired. So with that, maybe we could look at a couple of questions. This is a case one elderly lady lobar pneumonia, sodium 170, which of the following is the most appropriate?

Speaker 8 (00:51:47):
Next step, would you want to calculate the urine FENa to make sure she's not volume depleted or you want to give some more salt any body picks that? B is okay, if you do blood osmolality to confirm the hyperosmolality, do you want to do another to confirm. Next choice? do you want to give half saline and to correct the sodium, gradually half saline that's hypotonic, or you want to calculate deficit and to give half of the calculation and watch and see. Lastly, if you want to just initiate D5W and check sodium concentration in the beginning every two hours and then you want to correct the rate at the 0.5 milliequivalents per liter per hour and you aim to correct around 10 milliequivalents per day.

Speaker 8 (00:52:59):
Okay. So I think that's a good choice. And let's go over the answer. Hypernatremia in most of the cases is already presented as it's a very clear cut hyperosmolality situation in this patient I wouldn't do, recheck of blood osmolality. Secondly, you always want to assess volume status, for her. Her blood pressure's a bit on the high side and she got one liter of 0.9% saline and she doesn't have any volume congestion, but she is not volume depleted. Do you do the FENa? FENa has no use. I mean very little use in patients with hypernatremia because of the, occurrence of dehydration natriuresis this is a very well worked out mechanism, essentially it is easy

for you to remember is when the sodium is high, the kidney tend to turn on all mechanism, try to unload the sodium to avoid the further worsening osmolality.

Speaker 8 (00:54:14):

And that's sometimes even in the setting of volume depletion the urine sodium may not be low. So FENa wouldn't be very useful in this kind of a situation. So, the correct answer in this case is the E because you can calculate the water deficit. Give you a good idea of how we do empirically plan to start. There's a lots of assumptions. So you assume the patient has no urine output you assume she would not have bowel movement? There's lots of assumption, but the key is to start some fluids and then follow the level, see if you are on the right track. Second question is which statement regarding hypernatremia adaptation is correct. A immediate adaptation to prevent cell shrinkage is a related to ionic osmolyte influx

Speaker 8 (00:55:17):

Anybody pick that? Number two, cellular organic osmolyte require hours to days to accumulate and it's more toxic than ionic osmolytes. Okay. A couple of people. So C is the cellular osmolytes are imported from extracellular fluids. Imported. Imported. Okay. So last choice is a cell adequately adapted to hyperosmotic state can function normally. Anybody take that when they're adapted, they function kind of normal. Okay. We have some opportunity. So, the adaptation is kind of a sequential first is when water comes out that as threatening of cell shrinkage that's a lethal situation. So what happened was that the cell immediately opened up channels and as far as we know, the most, major player is NKCC1 and the sodium proton exchanger 1 because they are ubiquitously expressed and they increase the activity, powered by what sodium potassium ATPase.

Speaker 8 (00:56:53):

So you have that power driving the Jose and eventually you end up with the cells accumulating sodium chloride and potassium. But the problem is these ionic osmolytes are extremely toxic, bcause remember when we were in the lab, we want to denature protein, we just dropped some salt. It's a very toxic to DNA, very toxic to unfolding protein and it paralyzed the cell, so cell will not last for long.. And fortunately you have this second safeguard actually they are turned out simultaneously. But the thing is that the tonicity elongating binding new protein, it's a transcription factor and it

takes signals of osmolality and started to express, these proteins. So these are the targeting proteins, including the chaperones proteins that protected the cells from osmotic stress and eventually the cell will gather.

Speaker 8 (00:58:05):

These are the major osmolytes and these osmolytes are non charged. It's much less toxic. So the second choice is half right half wrong becaus, it takes, hours to days to generate these osmolytes but they are less toxic. They are not charged, so this is the urine osmolality. When the serum sodium is high, the first thing you look is the urine osmolality. If it's high or low the first patient was high and we thought there is no concentration defect and then, if it's low, that's like the ice kind of a situation. But even when cells adapted with the organic osmolytes replac. ionic osomolytes they are still not normal. These cells are overcrowded with all these, organic osmolytes Some of the organic osmolytes for instance, this one, the SMIT one, which is

Speaker 8 (00:59:15):

channel and it helps the cell gathers, myo-inositol but imyo-inositol it self has a function, sometimes it causes ionic fire to become irregular., so would affect the cellular excitability. And the another one is, for instance, aldose reductase . It will distort the redox situation and what happens is the cells, started to, generate a huge amount of reactive oxygen species plus the overcrowding. So the cell can survive but they will not function well. And you really need to correct them. Until you correct those osomin the cell, the cell will gradually die. So the immediate adaptation to prevent shrinkages ionic osmolytes, that's a good choice. Second choice says hour two days to generate organic osmolytes

Speaker 8 (01:00:31):

So that's correct, but they are less toxic. And third one is organic osmolytes, Some of them are generated in the cell, some of them are channels generated and imported outside of the cell, from the cell. So even they're adapted they would not be very normal you need to correct them. And which of the following regarding the correction, we are moving onto the correction, which following, regarding corrections correct. Calculate water deficit and based on the water deficit to guide your treatment. Of course we talked about that. You don't want to do that. Number two, acute hypernatremia sodium should be corrected at the rate of below one

milliequivalent per hour. Any body wants to take that? Number three C is for chronic hypernatremia, which is our first patient. The rate of corrections should be less than 10 milliequivalents per hour and may take 5, 6 days. Anybody take that? Less than 10, but may take 5, 6 days, anybody. And, the last one is you want to complete a correction, by 3 to 4 days. Andy body take that 3 to 4 days. Okay. So actually we really lack of,

Speaker 8 (01:02:18):

control the trial because, you know, I am an IRB person. I would never let you do a randomized control one slow and fast and generate that kind of study. So consequently these are all generated from retrospective and some of the studies are very old, for the correction of grater that then 0.5 milliequivalents per hour, this study was generated in neonates with sodium grater then 150, and if you go too fast in the chronic hypernatremia and they have a herniation and seizure and all kinds of other things, not in the adults. For the slow correction, we do have a retrospective study, a reasonable study, not a big number, small number and cohort studies showing that you cannot go too slow. If you go less than 0.25 the mortality is much higher. That's a 2011 study.

New Speaker (01:03:35):

so basically, you cannot go too fast, but you also could not go too slow, but too fast is from neonates. This is a study, a very small study, but it's very complete in the serial collection of data. Essentially tells you these patients, by day 5 ,you still haven't corrected their hypernatremia, all of them have permanent neurological damage and none of them survive. This is a relatively recent study looking at semi center study, all patient with hypernatremia on admission and then looking at by day 3 whether these patients corrected or not corrected and, turns out, for people with the corrected hypernatremia by day 3, they're having much lower mortality, mortality, difference is around 8 to10%. So, the persistent hypernatremia is one of the very significant independent predictor of deaths.

New Speaker (01:05:07):

and we recently looked at the Mayo data it's not published yet, but it's a similar situation. So when you look back, your correction, these are the neurono cells. It's nerve cuts tissue. So when you increase extracellular osmolality like a hypernatremic state, if you exaggerate this situation and the cell shrink volume come down, and if you do a 200 to 300 volume and

come down quite a bit, if you'd do 200, 250 volume, comes now a little bit less. But if you follow these neurono cells and you can wait wait for a long time, the cell has such a hard time to gather osmolytes like I told my fellow, when you make money, it's not easy to make money because in this kind of situation, cell has together osmolytes..

Speaker 8 (01:06:20):

So it's a really very hard situation. But if you, during the correction of hypernatremia, you started to reduce the osom. And then take this neuron again. you reduce osom then the cell start swelling a little bit. So I learned a bit more. If you have even reduced motes swollen less when you're reduce less. But then the cells started to leak the osmolytes and they're leaking is a very quick situation and most of the cells will get back to their previous situation by two days. And so if you are looking at this leaking of tourine and when the osmolality goes from change of a zero to a change of 10, which translate to sodium of change, maybe about 5 and you've already had a significant leakage of the tourine. So tourine takes days, to manufacture, but it quickly leaks out.

Speaker 8 (01:07:29):

So I think, the correction of hypernatremia is quite different from a hyponetrimia. It's not a reversible, not a symmetrical situation. And so for this patient, when 70, we like to correct in three days and you want to do it 10 milliequivalents and usually, you know, by serial monitoring, of their blood sodium and you can achieve a good result. So the second patient's Lithium do we know much about the lithium induced toxicity? Essentially lithium competes with sodium and magnesium. It's inhibits GSK 3 beta, one of the major situation is, it reduces the Cox in the tubules, but also inhibits sodium absorption in the proximal, in the sending lumen in the collecting duct so you have a huge amount of solute loss.

Speaker 8 (01:08:46):

And those patients usually have low blood pressure. And because of the increasing sodium in the tubule, they actually inhibit the afferent arteriole relaxation. You have Afferent arterioles reconstruction, so, the glomerular tend to be a bit more ischemic. it also inhibits the transduction from AVP, through the, downstream signaling. So essentially you have an AVP resistant state, so it's so resistant to AVP. So what you want to do is if you combine the lithium into one day dose and you would decrease the tubular

exposure. And if you add amiloride and you blocked the distal lithium enter into the cell because you can and, you could add a thiazide, it enhances a proximal lithium absorption.

Speaker 8 (01:10:05):

But that's the risk for lithium toxicity. That's not a major effect. Actually. Lithium is not very nicely studied to increase the aquaporin to expression for whatever reason and recently you can use indomethacin, but It's a kidney toxicity and you're really not want to do that recently acetazolamide. It's also being used. Acetazolamide has a multiple, functioning spot, but one of the effect is increasing, aquaporin to expression. This is a very, interesting case, published recently. If you give acetazolamide, the urine output reduces and then they sopped the acetazolamide urine out increases and they started again, it's coming down. There's a couple of very nice, mechanistic studies related to that. So the key points is the hypernatremia is extremely common, especially in at risk population, pediatric, geriatric critically ill patients and there's a very high rate of morbidity mortality. You don't want to leave them alone. You really need to work on, try to correct the hypernatremiac situation, the best sodium concentration somewhere once a day 142, and, that cause elimination and you don't want to rely on the formula to guide your treatment and the lethium, induced the effects that you can, do the steps that we talked about, that's it.

Speaker 10 (01:11:55):

[inaudible]

Speaker 1 (01:11:56):

we have time for one question. Is there any question from professor Qian Good morning. I'm a renal fellow in New Jersey. This is a question not just for all this dysnatremias when volume status is very difficult to assess, especially for those of us who are not critically care trained and don't have access to point of care ultrasound, what clinical parameters are you relying on most heavily for assessing volume status as like a final determinant? And is there a growing role for, ultrasound?

Speaker 1 (01:12:40):

So this is a $ million question. I've been intensivist for 15 years. I still struggle with some patients, some of patients are really easy to assess

their volume. They are really dry or Drudge really wet. You would know that . We generally, as you alluded to, we use ultrasonography, cardiac and IVC and longer ultrasonography per se for volume assessment before and after each bolus of volume we deliver to patient. So ultrasonography is safe, noninvasive, and in right hand the actually can produce significantly good results. Passive leg raising is a test that if you do it right, it can give you some information. There are obviously other tests that you can do as smaller, narrower group of patients, mechanical, eventually patient and so forth. Generally looking to have their edema or IVC or JVD. These are the classical evaluation of volume status.

Speaker 8 (01:13:41):
For the hyponetremia Sometimes it's very subtle and sometimes you could use uric acid fracture. A fractional excretion of uric acid and that's usually helps me to treat the SIDH I.

New Speaker (01:14:02):
if we look at data from the 1970s if you go back and read the report [

Speaker 1 (01:14:02):

Speaker 6 (01:15:27):
Great. So what also made me want to make a comment as far as the concern that you know, using all their [inaudible] for a very specific reason this and answer the question, right, you have a volume challenge. Am I going to have translation to a higher cardiac output? It has really, it's not a quick bolt to the point. I think that's being asked. You're asked here, what's the I can wire says so if I take it to just about anybody in the room here, especially healthy versus no cardiac conditions, but the oral side of their IVC collapsibility physiologic state, I would expect that. Right. But you know, when you're talking about using it and it's, I wouldn't use exercise a lot of caution and say we've got, what were you using all this now? What are you using it for and what evidence-base are you or are you basing your decisions on? You're using the modality because I frequently see all of the sound actually would not use directly.

Speaker 1 (01:16:26):

Absolutely. So do not fix a problem that does not exist. If you have a patient with normal hemodynamics and have IVC collapsibility do not give them fluid, you just create additional problem for the common prom gentleman here. There is a dissociation between total body volume, which we can ascertain by physical examination and effective blood volume,, which is what translates to cardiac output and perfusion of organs.we sometimes use lactate for, for perfusion state among patients who have significant edema. ultrasonography would help to you to get closer to that, state. But sometimes there is dissociation patients who have a lot of ID, more that very limited the intravascular volume or vice versa. They have appropriate intravascular volume they have [inaudible] skin and so forth. So there are some, some discrepancies between the two that can potentially customer,

Speaker 1 (01:17:42):

thank you. The dissection, as we both have a talk in the neighboring new room, I thank you for your participation.