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Telephone: +1-925-223-8242 Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com http://www.wjgnet.com

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Nephrology
ESPS manuscript NO: 30231
Title: Application of established pathophysiologic processes brings greater clarity to diagnosis and treatment of hyponatremia
Reviewer's code: 03522659
Reviewer's country: United States
Science editor: Jin-Xin Kong
Date sent for review: 2016-09-24 20:59
Date reviewed: 2016-10-04 10:33

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[Y] Accept
[Y] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

In brief the authors of the review article seek to highlight key points in pathophysiology of SIADH, reset osmostat and RSW and present an engagingly readable article on the faulty assumption of the existence of cerebral salt wasting syndrome while giving a simple algorithmic approach to diagnosis of hyponatremia giving a prominent role to FEurate in this process. I think the concept is very original and would definitely consider the article to be published with minor revision on some specific points. 1. Introduction needs to be limited to one paragraph. 2. Reference for case of hyponatremia with bronchogenic carcinoma in first paragraph on subheading on "evolution of new algorithm" is missing. 3. Some information on mechanism of why Feurate is not reduced with volume expansion in RSW would be instructive 4. What about the rule of fractional excretion of phosphate in diagnosis of RSW? 5. A little bit on the historical concept of CSW and the pitfalls in initial descriptions of cases of CSW may be given to underline the fallacious assumptions leading to this diagnosis 6. References in Table 3 are missing

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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Nephrology
ESPS manuscript NO: 30231
Title: Application of established pathophysiologic processes brings greater clarity to diagnosis and treatment of hyponatremia
Reviewer's code: 03368506
Reviewer's country: United States
Science editor: Jin-Xin Kong
Date sent for review: 2016-09-24 20:59
Date reviewed: 2016-09-26 22:04

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[Y] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[Y] Accept
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
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		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

I thoroughly enjoyed reading this manuscript. An idea presented is well backed-up by facts, literature and clinical reasoning. Well written with unnecessary details, physiologic concepts are well explained. The graphs are self-explanatory and clinically useful. Algorithms have a nice and logical flow. Much needed publication do decrease the existing confusion in this area of nephrology. I have only one suggestion to add another name for SIADH type D, "nephrogenic syndrome of inappropriate antidiuresis (NSIAD)", as this name is also used in the literature for gain-of function disorder. Excellent work.

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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Nephrology
ESPS manuscript NO: 30231
Title: Application of established pathophysiologic processes brings greater clarity to diagnosis and treatment of hyponatremia
Reviewer's code: 03523217
Reviewer's country: France
Science editor: Jin-Xin Kong
Date sent for review: 2016-09-24 20:59
Date reviewed: 2016-10-07 21:50

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[Y] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

In this review, Maesaka et al. propose differentiating SIADH to CSW/RSW by the use of FEurate. Hyponatremia is a very common finding that needs a methodical approach for both diagnosis & therapy: on the first hand, water restriction and/or vaptans are necessary, on the other, salt infusion is. Here, authors suggest deciphering both diseases not only by clinical clues but by using FEurate. To support this point of view, they argue many case reports and pathophysiological evidences. This manuscript arose several questions/remarks I would like authors to answer. Self-citation ratio is unusually high: 15/59 quotes (about ?). I do realize authors are very involved in diagnosis & treatment of hyponatremia: self-citation is not evidence, it is only consistency. Moreover, self-references are mostly case reports leading to make this review appear as a case reports collection and make it not suitable and easy to read (many repetitions). So, case reports are more illustrations than demonstration. In details: Page 6: "this unique relationship between FEurate & natremia" What should be the pathophysiologic relationship? In nephron, natremia (= water balance) is mostly regulated by AVP in collecting duct, whereas uricemia (& FEurate) is in proximal tubule… This

should be clearer in the manuscript. Page 7: the patient mentioned (ref 31) is told to exert hyponatremia (119mM) with spontaneous hypotonic urine (92 mOsm/kgH2O): so, it's not SIADH, it's water intoxication and normal renal response…I bet ADH secretion would have been close to…undetectable, as Uosm and ADH secretion are very closely correlated. Page 8 & Figure 2: do you correlate ADH secretion and FEurate? If so, ADH could directly act on FEurate (i.e. proximal tubule PT)? What should be the physiological mechanism? Have ADH receptor been reported to be expressed by PT? Shouldn't it be mediated only by the correction of extracellular compartment? I'm not completely convinced by the figure 2: was FEurate measured at the same time all days? Page 12: all over the manuscript, authors argue that "extracellular status cannot be accurately assessed by usual clinical criteria" but illustrate their case reports by such "clinical criteria" as of orthostatic hypotension and/or tachycardia… Water restriction should not be an aim; the true one should be water balance negativation: the amount of water restriction should be correlated to osmotic ballast daily load… Page 17: what does mean SAH? SIADH? Page 20: hyponatremia is the most common electrolyte disorder Page 29: table 2 starts with hyponatremia, if FEurate is >11% that leads to "normonatremia"…something is weird and should be corrected and/or clarified. Page 30 table 3: where are the data from? How were them collected? Authors should distinguish sex, age, dietary salt intake and many other cofounders that could make the interpretation of FEurate hazardous (cf. Steinhauslin JASN 1994 & Cappuccio JAMA 1993). Moreover, un unpublished work has shown nycthemeral modifications of FEurate during a swiss (Lausanne) study in the general population. Authors should attenuate the importance of FEurate. Page 32 figure 1: regarding to the poor reproducibility of plasma AVP measurements, authors should refer (also) to Uosm. Do we really need AVP measurement for the diagnosis of SIADH?

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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Nephrology
ESPS manuscript NO: 30231
Title: Application of established pathophysiologic processes brings greater clarity to diagnosis and treatment of hyponatremia
Reviewer's code: 01200577
Reviewer's country: Italy
Science editor: Jin-Xin Kong
Date sent for review: 2016-09-24 20:59
Date reviewed: 2016-10-17 01:53

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
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		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

In this paper Maesaka et al., starting from the observation that clinical examination is not a valuable tool to assess volume status, propose the use of FEurate as an additional strategy to differentiate SIADH to CSW/RSW. I think that the initial observation is correct and the introduction on new tools for managing hyponatremia might be useful for clinicians. Nevertheless, although the reported approach seems interesting, I found some points that, in my opinion, should be clarified: Major considerations 1. The authors state that they adopt a pathophysiological approach, but they don't explain the pathophysiological mechanisms underlying the relationship between natremia and FEurate. Indeed, they report a case series that, in their opinion, should sustain their hypothesis but there is not a clear explanation of any mechanism. I think that a new paragraph on this specific issue could add important information for the readers. 2. Because of its structure (a collection of case reports) the paper might be difficult to follow and in some cases it is repetitive. 3. I don't understand how they set 11% as a threshold to differentiate SIADH from CSW/RSW. Was it derived from case reports or from more structured studies? Equally, I don't understand the relation between

normonatremia and FEurate > 11% (table 2-which is actually a figure). Is it supported by some data? What does it mean? 4. There is a general lack of references in tables and figures (especially table 3-what are the sources of that data? and figures 3,5,6). 5. Figure 1 is adapted from Robertson GL Regulation of arginine vasopressin in the syndrome of inappropriate antidiuresis. Am J Med 2006;119(7 Suppl 1):S36-S42. I think that authors should clearly indicate this reference and require permission to publish that figure. Minor considerations: 1. It should be noticed that some authors prefer the term SIAD (syndrome of inappropriate antidiuresis) instead of SIADH.