Format for ANSWERING REVIEWERS

January 12, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: wjn ESPS 15495-revised.doc).

Title: Pharmacokinetic and pharmacodynamic considerations of antimicrobial drug therapy in cancer patients with kidney dysfunction

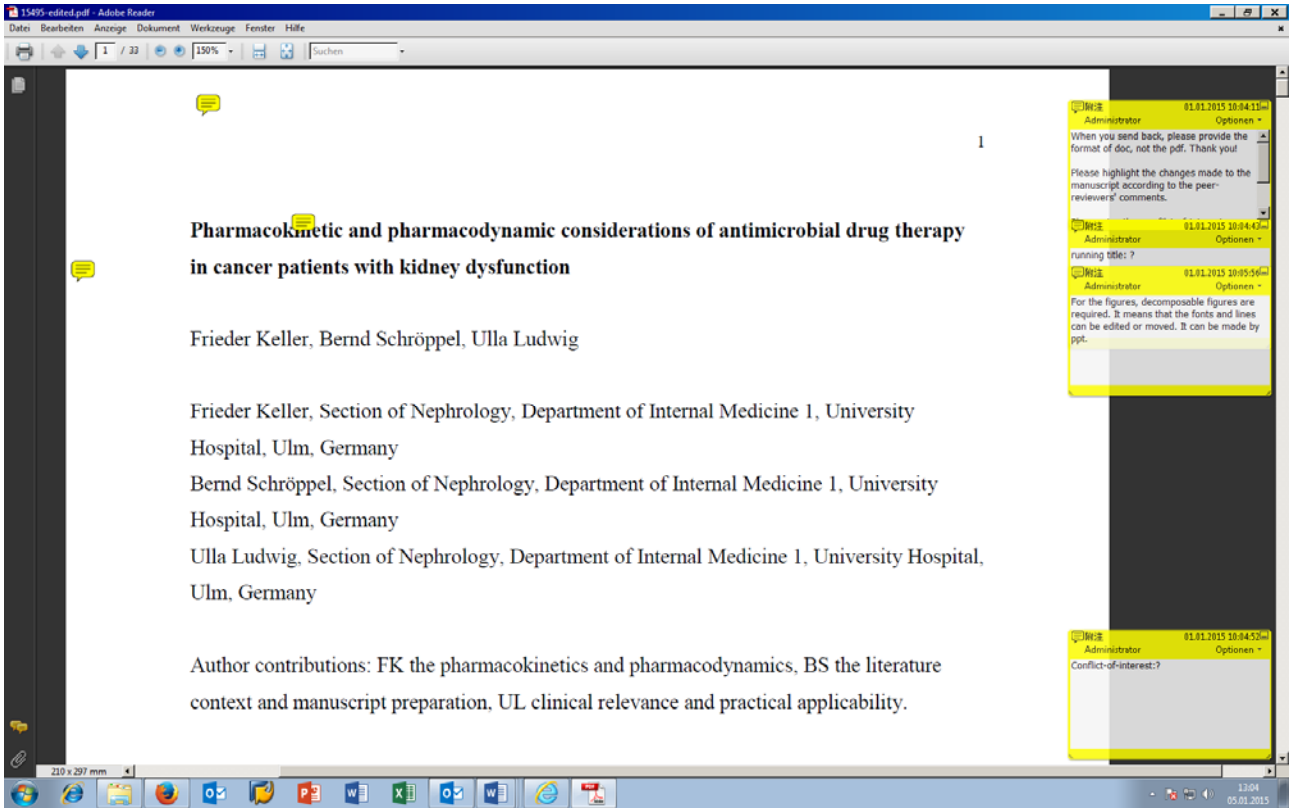
Author: Frieder Keller, Bernd Schröppel, Ulla Ludwig

Name of Journal: *World Journal of Nephrology*

ESPS Manuscript NO: 15495-revised

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

- ⇨ … according to a minireview as mentioned by the editorial administrator: we send a .doc file, a marked version, we added the running title and the figures as .ppt files.



2 Revision has been made according to the suggestions of the reviewer

Reviewer 503334

A nice paper with an interesting topic! I had an excellent and very educative reading! However, how can the pharmacokinetic database (NEPharm) be used to guild the dose adjustment is not clear. Authors should provide us more solid evidence (for example, some cases or data) to support the use of the database. For example, for the 73 years old female in the case report, how did you know the manufacturer recommend 500 mg twice daily is under dosed, while 1000 mg every 12 hours is optimal ? Did you measure the serum drug concentration? The paper will be significantly strengthened, if there is a step-by-step guideline on how to determine and adjust the dose.

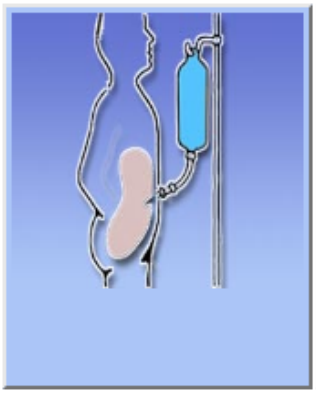
- ⇨ The meropenem example is given within the case report for the dosing rules and for the post-hemodialysis dose. In addition, the statement that the dose recommended by the manufacturer might be too low has been taken from the cited reference [6] – which is now made more clear.
- ⇨ To support our statement on meropenem we depict here the dosing recommendation by the producer

Meropenem Merrem ® - Renal dosing

Usual Dosing (Adults)

Usual: 1 gram IV q8h.
Complicated skin/skin structure infections: 500 mg IV q8h.
Intra-abdominal infections: 1 gram IV q8h.
Meningitis: 2 gram IV q8h.

Renal Dosing



[CRCL >50]: no change

[26-50]: Usual: 1 gram q12h.
(UTI, skin/ skin structure infections): 500mg q12h

[10-25]: Usual: 500 mg q12h.
(UTI, skin/ skin structure infections): 250mg q12h

[<10]: Usual: 500mg q24h.
(UTI, skin/ skin structure infections): 250mg q24h

- ⇨ Unfortunately, we did not measure the meropenem concentrations is this case.
- ⇨ We give now the example of ampicillin for dose adjustment to GFR and for the post-dialysis dose to explain the use of Table 1.

Reviewer 503233
very good, no changes required

- ⇨ Thank you

Reviewer 503339
While the subject addressed is unquestioned as worthy of study and the answers gained from such study will be clinically important, it its present form, there is too much speculation and only minimal data supporting the use of equations proposed. What would be most constructive is a Step-by-Step procedure for determining the dose of various antimicrobial regimens during the course of treatment of genitourinary malignancies. That the dose adjustments were of value would have to be supported by Treatment and Control Groups in which the superior value of the dose adjustment regimens advocated is evident. Bssed on current knowledge, the dose adjustment advice provided is mainly speculative.

- ⇨ Again, our approach now is better illustrated step-by-step using the examples of ampicillin (twice) and meropenem (twice).
- ⇨ Indeed, we once have already planned the requested clinical study with a control group. But this is impossible to perform for us. Such a trial must be a prospectively randomized controlled trial that needs to be designed for kidney patients and ICU patients, for different anti-infective drugs, and this needs at least two dosing alternatives to be compared e.g. Dettli 2 and Kunin. This must be a multicenter trial and hard clinical end points must be investigated – such as in-hospital mortality. There are many confounding factors that must be controlled, decreasing or restituting kidney function, renal replacement therapy, surgical or medical ward, number of failing organs, respirator, co-morbidity such as diabetes, pulmonary obstruction, malignancies …. co-medication such as immunosuppression, anticancer therapy … It is difficult to obtain the singed consent to such an interventional trial from the very sick e.g. ICU patients. Lack of money and logistic difficulties made us resign and abstain from such a trial.
- ⇨ However, there is some literature that we have cited and commented on demonstrating the existing clinical experience with different dosing regimens in patients with kidney dysfunction: e.g. references [6, 9, 26-28, 31, 33, 36-46, 48-53, 57, 58, 60, 64 and 65].

Reviewer 503279
This is a nice work but needs to be reviewed by a native English language expert and should be carefully revised for some typing errors and few unclear sentences that need to be rephrased.

- ⇨ The English has read and been improved by a commercial agency. The copy of the certificate, I enclose here.

In addition, we have made minor changes in the text, in the figures and in the table to update the paper and to improve the readability. We send the revised paper and a version of the revised paper where all changes have been marked. In addition, the signed copyright assignment is submitted.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Nephrology* .

Sincerely yours,

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