Author’s response to reviews

Title: Biopsy-proven vancomycin-induced acute kidney injury: a case report and literature review

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Authors:
Anri Sawada (anri-sawada@nms.ac.jp)
Dear Dr. Steven Weisbord, Editor of BMC series

We appreciate meaningful comments from reviewers, and your editors for our manuscript entitled "Biopsy-proven vancomycin-induced acute kidney injury: a case report and literature review" (Manuscript number BNEP-D-17-00525R1). Herein, I am going to send a revised manuscript that would hopefully be responded to all comments by you and reviewers. Each correction in manuscript was highlighted in red color.

We look forward to hearing from you regarding our submission. We would be glad to respond to any further questions and comments that you may have.
Response to M. Barry Stokes (Reviewer 1)

We wish to express our deep appreciation to you to evaluate our manuscript entitled "Biopsy-proven vancomycin-induced acute kidney injury: a case report and literature review" (Manuscript number BNEP-D-17-00525R1).

Our responses to your comments and revised manuscript are as follows:

Comment:

The paper is well-written but does not offer new insights into the pathophysiology of vancomycin-induced AKI. It is indeed possible (but not proven) that HD had a direct therapeutic benefit by reducing levels of vancomycin.

However, it is unclear if the biopsy findings can be attributed to vancomycin, rather than ampicillin/sulbactam, as the biopsy was performed 12 days after vancomycin was discontinued, and the patient developed a rash while receiving ampicillin/sulbactam. Thus, it seems possible that even if the patient had vancomycin induced AKI initially, he may also have developed AIN from other antibiotics which would explain the renal biopsy findings.
Response1:

We agreed that the influence of ABPC/SBT should be considered. According to your suggestion, we replaced the sentence P4 L2-4, P9 L4-5, P11 L6-11 and P11 L16 - P12 L3 as below:

P4 L2-4

(Version 0)
Renal biopsy showed acute tubular necrosis and acute interstitial nephritis, mainly in the medullary rays (medullary ray injury).

(Version 1)
Renal biopsy showed acute tubular necrosis and focal acute interstitial nephritis, mainly in the medullary rays (medullary ray injury).

P9 L3-4

(Version 0)
In summary, the kidney biopsy showed mild diabetic nephropathy with AIN and ATN.

(Version 1)
In summary, the kidney biopsy showed ATN and focal AIN with mild diabetic nephropathy.

P11 L7-12

(Version 0)
Meanwhile, synergistic toxicity of VCM and other antibiotics such as PIPC/TAZ, cefepime, aminoglycoside should be considered in the current case as shown in previous studies [21, 22, 23].
Meanwhile, it is difficult to define what is cause of VCM-induced AKI in clinical cases; synergistic toxicity of VCM and other antibiotics such as PIPC/TAZ, cefepime, aminoglycoside should be considered in the current case as shown in previous studies [29, 30, 31]. Other multiple drug usages could affect VCM pharmacokinetics. Furthermore, VCM-induced AKI is more likely to occur in pre-existing renal disease [3].

P11 L17 – P12 L5

No significant sign of other renal diseases was detected except mild diabetic nephropathy and VCM-induced ATN and AIN.

The renal biopsy showed ATN and localized AIN with mild diabetic nephropathy, which suggested that the main cause of AKI was considered to be VCM induced ATN and AIN. AIN caused by ABPC/SBT should be considered, because this case showed rash. Although ABPC/SBT frequently cause rash (1.2%), severe AKI is rare in ABPC/SBT usage by itself [33, 34].

Response2:

Renal biopsy is not standard for VCM induced AKI. But there are a few reports showing usefulness of renal biopsy. In this case, renal biopsy result was commit to the differential diagnosis and treatment option. We believe this report suggest importance of renal biopsy to assess prognostic and therapeutic option for the cases of VCM-induced AKI. To show our aim more clearly, we replaced sentence P11 L15-16 and P12 L10-15.
We performed renal biopsy to establish a differential diagnosis for the patient’s skin rash, poor controlled type 1 DM, proteinuria on admission and continuous oliguria.

Renal biopsy was necessary in our case, because we need to differentiate other renal diseases such as glomerulonephritis and diabetic nephropathy for proteinuria on admission and continuous oliguria.

Oral prednisone therapy was not attempted because he had poor controlled DM, frontier gangrene. Renal biopsy result (localized AIN) was commit to our decision on no steroid use in the retrospective view. However, if AIN lesion is more expanded, oral prednisone should be considered to treat not only for VCM- induced AKI but for possible side effects of ABPC/SBT.

Meanwhile, as you mentioned, it is difficult to prove what HD therapy contributed to reducing plasma levels of vancomycin. However, as we referred in the manuscript, some reports showed that frequent HD with high-flux filters could be useful in pediatric cases [7, 35]. In our case, we believe that frequent HD with high-flux filters contributed to his urine volume increase, in accordance with decreasing of his plasma VCM levels. To our knowledge, there are no reports that show usefulness of VCM removal by frequent HD with high-flux filters in adult case. We
believe this report offers a new insight that frequent HD with high-flux filters is useful for VCM induced AKI even for adult patients.

Response to Ying Zhou (Reviewer 2)

We wish to express our deep appreciation to you to evaluate our manuscript entitled "Biopsy-proven vancomycin-induced acute kidney injury: a case report and literature review" (Manuscript number BNEP-D-17-00525R1). Our responses to your comments and revised manuscript are as follows:

Comment 1:
Please supplement the patient's medication and family history appropriately.

Response 1:
According to your suggestion, we added patient's medication and family history in P 6 L 5-10.

(version0)

His blood pressure was well controlled with an aldosterone receptor blocker, and he had diabetic retinopathy (simple type).

(version1)

His blood pressure was well controlled with an aldosterone receptor blocker. DM control was poor (haemoglobin A1c 9.0-10.0 %) under intensive conventional insulin therapy. His diabetic retinopathy was simple type. Pregabalin, duloxetine and mexiletine were also used for diabetic neuropathy. His family history was not significant except cerebral infarction in his grandmother.
Comment 2:

The white blood cell count on page 6 is inconsistent with that in Table 1 (page. 21).

Response2:

We corrected blood cell count in Table 1 (P26).

Comment 3:

The author may show the adjustment of vancomycin dosing regimen in Fig.1, which helps to understand the changes in vancomycin concentrations.

Response3:

According to your suggestion, we showed vancomycin dosing difference in Fig.1.

And the following statement was added to the legend; ‘Intravenous vancomycin dosages were 3.0 g/day, then increased to 4.5 g/day.’

Comment 4:

Are there any follow-up results after discharge?

Response4:

According to your suggestion, we added follow-up results of serum creatinine in P 8 L 8.

(version0)
Eight months later, his sCr was decreased to 109.6 μmol/L.

Comment 5:

Please supplement the diagnostic criteria of VCM-AKI in discussion.

Response 5:

According to your suggestion, we added diagnostic criteria of vancomycin induced acute kidney injury in P 9 L 12-16.

VCM-induced AKI is initially diagnosed when 50% sCr (or 44.2 μmol/l) elevation from baseline is detected in at least two different time points after administration of VCM treatment [15]. However, many of recent studies are committed to the definition and classification of AKI of RIFLE, AKIN and KDIGO criteria [16, 17, 18].

Comment 6:

In addition to prompt treatment, the prevention of VCM-AKI is equally important. The author illustrated that current recommendations for the prevention or treatment of VCM-AKI were drug monitoring of plasma vancomycin levels using area under the curve and drug withdrawal. Could
the author explain in detail what measures should be taken corresponding to different vancomycin concentrations and AUC levels? In addition to the monitoring of vancomycin, is it necessary to monitor serum creatinine?

Response6:

We appreciate your important suggestion. We agreed that the prevention of VCM related AKI is equally important. We added the description about the prevention and early diagnosis of VCM related AKI in P10 L1-11 and P14 L1-3.

P9 L17 - P10 L10

(version0)

No description

(version1)

Plasma VCM level should be controlled in the appropriate range to prevent VCM- induced AKI. Plasma VCM level could be measured with therapeutic drug monitoring (TDM), such as VCM trough and area under the curve (AUC). However, VCM trough and AUC might be insufficient for prediction of VCM-induced AKI in large population study [19]. Moreover, available TDM guidelines still need optimizations to establish a more reliable VCM-TDM strategy in accordance with risk factors according to risk factors [20]. Previous studies showed that minimal sCr elevation is associated with prognosis of AKI [21], and intensive monitoring of urine output could be useful for AKI diagnosis and better outcomes [22]. More careful monitoring should be used to detect AKI as soon as possible in VCM usage.
This case suggests that more careful VCM-TDM and intensive monitoring of sCr and urinary output to detect AKI should be considered in VCM usage.

Comment 7:

What can we learn from this case? Should the prevention of VCM-AKI be strengthened? In high-risk VCM-AKI cases, whether vancomycin should be avoided in combination with nephrotoxic drugs?

Response 7:

We believe that this case report suggested renal biopsy and frequent dialysis are prognostic and therapeutic option for high risk VCM induced AKI cases. VCM have established effectiveness for methicillin-resistant Staphylococcus aureus and coagulase-negative strains. We consider that VCM should be used under careful VCM-TDM, intensive monitoring of sCr and urinary output. It is necessary to be careful to increase VCM dose in combination with nephrotoxic agents.

Other corrections

• We modified some minor changes of Figure 1-3.

• We added Age and sex in Table.2 (P27)
• We replaced sentence of abstract in P3 L11 and P3L18

P3 L11

(version0)
plasma vancomycin levels using area under the curve and drug withdrawal.

(version1)
plasma vancomycin levels using trough level and drug withdrawal.

P3 L18

(version0)
his plasma level of vancomycin

(version1)
his plasma trough level of vancomycin

• We added sentence about target of plasma trough level of VCM in P7 L4-6.

(version0)
Because his trough VCM level was still low (9.24 μg/mL) and sCr stable (83.1 μmol/L) on day 3, intravenous VCM increased to 1.5 g every 8 h.

(version1)
Because his trough VCM level was still low (9.24 μg/mL, 15-20 μg/mL is for complicated infections [12]) and sCr stable (83.1 μmol/L) on day 3, intravenous VCM increased to 1.5 g every 8 h.
The six references were “Not Validated”. So, we describe six reference number in revised edition and the PMID (indexed for MEDLINE) or doi code.

10: PMID: 20391819

14: PMID: 13542649

16: doi:10.1038/kisup.2012.2

22: PMID: 28527880

28: PMID: 8975151

38: PMID: 9710347