Peer Review File

Article Information: http://dx.doi.org/10.21037/atm-20-4005

Comment 1: There was a similar report (Antimicrob Agents Chemother. 2012 Dec;56(12):6181-5) in the PubMed. What is the novel idea in the paper? Please elaborate in the introduction.

Reply 1: Thank you for your comments and constructive suggestions. We have read the report (Antimicrob Agents Chemother. 2012 Dec;56(12):6181-5) carefully. This report demonstrated an inverse association between hemofiltration rates and serum vancomycin concentrations; increases in hemofiltration rates significantly correlated with reductions in trough concentrations. There are several differences between this report and our study. First, the objects were different. Frazee *et al.*'s study (Antimicrob Agents Chemother. 2012 Dec;56(12):6181-5) was performed in critically ill adults, all of whom received continuous venovenous hemofiltration (CVVH) treatment; while we divided critically ill children into CVVH and non-CVVH therapy groups, only patients with acute kidney injury (AKI) received CVVH treatment. Second, the aim was different. The primary aim of Frazee *et al.*'s study was to investigate the effects of different hemofiltration rates (≤30 ml/kg/h or >30 ml/kg/h) on achievement of therapeutic trough concentrations (10-20 mg/L) in patients with CVVH therapy. However, the dominating aim of our study was to investigate CVVH effects on vancomycin trough concentrations in critically ill children between CVVH

and non-CVVH groups. To our knowledge, this is the first survey to investigate the effects of CVVH therapy on vancomycin trough concentrations with the vancomycin dosage of 40-60 mg/kg/day in critically ill children. We showed that CVVH therapy affected vancomycin trough concentrations and was associated with supratherapeutic trough concentrations (>20 mg/L) with the vancomycin dosage of 40-60 mg/kg/day. Pediatric Risk of Mortality (PRISM) III scores ≥28 may serve as an independent risk factor of supratherapeutic trough concentrations for CVVH therapy children.

Change in the text: We have described the novelty of this study in the revised manuscript and indicated the changes in red (see revised manuscript page 7 line 133-136).

Comment 2: In the introduction, please enrich the research progress of the vancomycin.

Reply 2: Thank you for your constructive comments and suggestions. Vancomycin is a major glycopeptide antibiotic against most Gram-positive infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE) and amoxicillin-resistant *enterococci*. Additionally, vancomycin possesses activity against *Clostridium difficile* and can be used to treat pseudomembranous enterocolitis in its oral form. In terms of pharmacology, vancomycin is bactericidal and exhibits time-dependent killing, meaning that the effect of the drug antibacterial activity is pharmacokinetically dependent on the time that the serum concentration of vancomycin is above the

minimum inhibitory concentration (MIC). In recent years, studies were conducted to explore how to achieve trough concentrations in critically ill patients undergoing CVVH therapy. A prospective observational study suggested that continuous infusion vancomycin (CIV) achieved target concentrations more rapidly and consistently when critically ill adult patients received CVVH treatment (J Antimicrob Chemother 2018;73:199-203).

Change in the text: We have enriched the research progress of the vancomycin in the revised manuscript and indicated the changes in red (see revised manuscript page 5 line 89-93, page 5 line 106-109 and page 6 line 131- page 7 line 133).

Comment 3: Please supplement the introduction of trough concentration in the introduction.

Reply 3: Thank you for your constructive suggestions. Reaching therapeutic trough concentrations is one of the most important factors related to the successful treatment outcome in critically ill patients. Lower vancomycin trough concentrations are associated with increased mortality and drug resistance, while higher trough concentrations can induce vancomycin-associated nephrotoxicity. Therefore, the range of the therapeutic vancomycin trough concentration is undoubtedly important. Both Infectious Diseases Society of America (IDSA) and the Japanese Society of Chemotherapy recommend a vancomycin trough concentration of 10-20 mg/L: 10-15 mg/L for uncomplicated infections and 15-20 mg/L for serious infections (including bacteremia, infective endocarditis, osteomyelitis, meningitis and pneumonia). The

Chinese Pharmacological Society recommends 10-15 mg/L as the therapeutic trough concentration for adult patients and 10-20 mg/L for severe MRSA infections.

Change in the text: We have supplemented the introduction of trough concentrations in the revised manuscript and indicated the changes in red (see revised manuscript page 6 line 115-123).

Comment 4: How to determine the vancomycin dosage?

Reply 4: Thank you for your comments. The attending pediatric clinicians prescribed an individualized initial vancomycin daily dosage in accordance with pediatric references and drug instructions. The adjustment of vancomycin dosage regimen was recommended by therapeutic drug monitoring (TDM). The TDM target for the vancomycin trough concentration was 10-20 mg/L.

Change in the text: We have described the methods of determining vancomycin dosages in the revised manuscript and indicated the changes in red (see revised manuscript page 9 line 188-196).

Comment 5: How many cases in CVVH group and non-CVVH group? Please illustrate clearly in the methods.

Reply 5: Thank you for your suggestions. During the study period, 445 patients received evaluation for eligibility. 119 patients were eventually included according to inclusion and exclusion criteria, of whom 35 patients in CVVH group and 84 patients in non-CVVH group. Detailed information was presented in the *Figure 1*.

Change in the text: We have illustrate the cases in CVVH group and non-CVVH group in the revised manuscript and indicated the changes in red (see revised manuscript page 3 line 57-58).

Comment 6: The measure methods of serum trough concentration should be described detailed in the methods.

Reply 6: Thank you for your constructive suggestions. About 2 ml blood samples were obtained at steady state conditions, 0.5±0.5 hour prior to the fourth or fifth dose to determine the trough concentration. The vancomycin trough concentration analysis utilized chemiluminescence immunoassay method (Abbott Laboratories, Chicago, IL, USA). The assay has an analytical range of 0.0-100.0 mg/L, and the between-run coefficient of variation is <15% throughout the analytical range. A central laboratory was assigned to test all the blood samples within 24 hours, and intra-batch and inter-batch quality control was performed in accordance with the China National Accreditation Service for Conformity Assessment standard.

Change in the text: We have described the measure methods of serum trough concentrations in detail in the revised manuscript and indicated the changes in red (see revised manuscript page 10 line 200-206).

Comment 7: The figure format of table 1, 2 and 3 should be changed to table format or word format.

Reply 4: Thank you for your constructive suggestions. We are very sorry for our incorrect format. We have changed the figure format of table 1,2 and 3 to table format

(see revised table 1, 2 and 3).

Comment 8: How to identify supratherapeutic trough concentration? How to calculate PRISM □ scores? How to determine the optimal cutoff?

Reply 4: Thank you for your comments. We identified trough concentrations >20 mg/L as suprathrapeutic trough concentrations in accordance with IDSA guideline recommendations (Clin Infect Dis 2011;52:e18-55). We calculated PRISM □ scores at the time of extracting serum vancomycin trough concentration samples according to a study (Crit Care Med. 1996; 24:743-52). Receiver operating characteristic analysis was employed to find the optimal cutoff point of PRISM III scores using the maximum Youden's index and calculated sensitivity and specificity with 95% confidence intervals (CIs) for the optimal cutoff point.

Change in the text: We have described the methods of the identification of supratherapeutic trough concentrations and the methods of calculating PRISM □ scores and the methods of determining the optimal cutoff value in the revised manuscript and indicated the changes in red (see revised manuscript page 9 line 178-185 and page 11 line 228-231).