Antimicrobial Stewardship News

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Vancomycin and piperacillin-tazobactam

Bad for your patients' kidneys?

The popular empiric combination of intravenous vancomycin (vanc) and piperacillin-tazobactam (pip-tazo) is under scrutiny for causing acute kidney injury (AKI). This newsletter reviews the vanc/pip-tazo literature, outlines other modifiable risks, and gives strategies to minimize nephrotoxicity in patients receiving vanc/pip-tazo.

Literature review

Vancomycin alone can cause AKI in 5-30% of people who receive it. Multiple studies have been published to evaluate if the combination of vanc and pip-tazo is associated with AKI; results are mixed. [1]

For example, Burgess et al retrospectively evaluated the incidence of AKI in 92 patients who received vanc/pip-tazo and compared it to the incidence of AKI in 99 patients who received vancomycin monotherapy. [1] Nephrotoxicity developed in 15/92 (16.3%) of patients receiving combination therapy compared to 8/99 (8.1%) patients receiving vanc monotherapy (p=0.04). Furthermore, the authors noted a vancomycin trough >15 as an additional risk factor.

Use Extended Infusion piperacillin-tazobactam when possible.

However, after adjustment for this risk, vanc/pip-tazo was still associated with an increased risk of AKI compared to vanc monotherapy (odds ratio 2.48, p=0.03). The authors concluded that co-adminstration of vanc and pip-tazo resulted in an increase in AKI.

Gomes et al evaluated whether β-lactam selection affected AKI incidence in patients receiving vancomycin.[2] The authors performed a retrospective matched cohort study of 112 patients receiving cefepime/vanc and 112 patients receiving pip-tazo/ vanc, and after adjusting for potential confounders, the odds of developing AKI was 5.67 higher in the vanc/pip-tazo group compared to the vanc/cefepime group (odds ratio 5.67, 95% CI 1.66-19.33). The authors concluded that the addition of pip-tazo increased AKI risk compared to cefepime in patients receiving vancomycin.

Similarly, Hammond et al evaluated whether β-lactam selection (pip-tazo or cefepime) affected AKI incidence in critically ill patients receiving vancomycin. [3] The authors included 49 critically ill patients receiving vanc/pip-tazo and 73 critically ill patients receiving vanc/cefepime in the analysis. These authors found no significant difference in the incidence of AKI between the vanc/pip-tazo and the vanc/cefepime groups, even after adjusting for confounders

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- Please help us in welcoming 2 new members of the DASON team! Matthew Ryan is our DASON Clinical Research Coordinator. Travis Jones is a new ID-trained pharmD working with DASON liaisons.
- MARK YOUR CALENDARS! The DASON Continuing Education series program titled "Incorporating Procalcitonin testing in Sepsis Protocols" will be held on August 4 and 11 via webinar. Emails for registration will be circulated soon.
- Please return your comments on the Centers for Medicare and Medicaid proposed Conditions of Participation to Libby at libby.dodds@duke.edu
- The DASON website now has a link to the National Quality Forum Antimicrobial Stewardship Playbook.

(32.7% vs. 28.8%, p=0.761). The authors concluded that in critically ill patients, the risk of AKI was the same in patients receiving pip-tazo/vanc and cefepime/vanc.

Predictors of AKI development

Karino et al further investigated the risk of AKI in 320 patients receiving vanc/pip-tazo. [4] In this well done nested case control study, the authors examined the relationship between AKI and pip-tazo infusion type (extended infusion (EI) vs. standard infusion (SI)). The authors concluded that EI did not increase AKI incidence when compared to SI (33.1% vs. 32.5%, p=1). Therefore, the authors concluded that EI is a safe infusion modality for pip-tazo.

Moreover, Karino et al identified multiple other independent predictor of AKI development, including receipt of a vanc loading dose, receipt of concomitant nephrotoxins, and treatment of a documented Gram-positive infection as. The authors also found

Minimize other nephrotoxic agents when using piperacillin-tazobactam.

a meaningful association between the duration of vanc/pip-tazo therapy and the development of AKI. Interestingly, the daily rates of AKI in patients receiving vanc/pip-tazo were <10% on day 2 and 3. However, on day 4, the risk of AKI increased to 10.7%, and then to 19.5% on day 5. Almost 40% of the observed AKI occurred on days 4 and 5!

Strategies to reduce nephrotoxicity

DASON recommends continued careful and deliberate use of vanc/pip-tazo in patients who require broad spectrum empiric antibiotics. Overall, we believe the literature supports the belief that vanc/pip-tazo combination therapy increases the risk of AKI development more than just the risk from vanc alone. This risk can be decreased, however, with attention to the following modifiable risk factors:

- Avoid co-administration of other nephrotoxic agents
- Avoid unnecessary vancomycin loading doses
- Avoid prolonged combination therapy

DASON Recommendations

We recommend the continued use of vanc/pip-tazo with reservations. First, patients placed on empiric combination therapy should be frequently reevaluated for signs of AKI and, importantly, the need of continued combination therapy.

Re-evaluate frequently and discontinue combination therapy within 72 hours.

Second, we recommend continued use of extended infusions of piperacillin-tazobactam, as EI do not increase AKI greater than standard dosing, but do optimize drug delivery.

Third, we recommend minimizing other nephrotoxic medication exposure to patients receiving vanc/pip-tazo.

References

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2. Gomes, D.M., et al., *Comparison of acute kidney injury during treatment with vancomycin in combination with piperacillin-tazobactam or cefepime.* Pharmacotherapy, 2014. **34**(7): p. 662-9.
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