Feb 11 2018 06:18:23:459AM

RE: CCMED-D-18-00284, entitled "Piperacillin-tazobactam: extended infusion vs continuous infusion"

Dear Dr. Messori,

Thank you for your letter entitled "Piperacillin-tazobactam: extended infusion vs continuous infusion." We are pleased to accept this for publication in the next available issue of Critical Care Medicine. It is important that we have your current contact information so that the page proofs reach you promptly. If your address, email, or telephone or fax numbers change, please notify us as soon as possible by e-mail at journals@sccm.org or by telephone at 847-827-6869.

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Once again, we appreciate your support of Critical Care Medicine.

Sincerely,

Timothy G. Buchman, PhD, MD, MCCM
Editor-in-Chief
Critical Care Medicine
**Critical Care Medicine**

**Piperacillin-tazobactam: extended infusion vs continuous infusion**

---Manuscript Draft---

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31 January 2018

The Editor
Clinical Care
Medicine

Dear Editor,

We would like to submit the enclosed manuscript (entitled “Piperacillin-tazobactam: extended infusion vs continuous infusion”) for publication as an online Letter to the Editor. All authors have read and approved the submitted manuscript; the manuscript has not been submitted elsewhere nor published elsewhere in whole or in part.

Thank you for your kind attention.

Sincerely,

Dr. Andrea Messori

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Letter to the Editor:

Piperacillin-tazobactam: extended infusion vs continuous infusion

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The meta-analysis by Rhodes et al (1) confirms that a prolonged infusion of piperacillin-tazobactam over 3 to 24 hours, compared with bolus administration, reduces mortality in patients with sepsis and improves the cure rate. Since the Summary of Product Characteristics of this agent only includes a bolus administration, the findings by Rhodes et al raise the question of whether this compound, when used as a prolonged infusion, is stable in vitro over more than 3 hours up to 24 hours. Data from the literature (2,3) are not conclusive on this point because the stability of the drug depends on the presence of EDTA and the co-administration of other agents. Anyhow, an adequate stability is more likely at 3-4 hours (extended infusion, $E_{inf}$) than at 24 hours (continuous infusion, $C_{inf}$).

In evaluating mortality, Rhodes et al have included 8 studies employing $C_{inf}$ and 10 studies employing $E_{inf}$. If one considers $C_{inf}$ vs $E_{inf}$ as a covariate, a metaregression (based on the same data and the same random-effect model; computations made by the Open Meta-Analyst software, http://www.cebm.brown.edu/openmeta) shows that the odds-ratio (OR) for mortality is numerically in favor of $C_{inf}$, but is far from statistical significance (OR for $C_{inf}$ vs $E_{inf}$=0.97; 95%CI: 0.65 to 1.45; p=0.89). If one examines the absolute risk difference of $C_{inf}$ or $E_{inf}$, each compared with the controls, its value is −5.1% for $C_{inf}$ (95%CI: −9.3% to −0.9%) and −3.3% for $E_{inf}$ (95%CI: −6.4% to −0.1%). These findings show that the absolute difference in mortality for $E_{inf}$ vs $C_{inf}$ can be estimated at +1.8% [with 95%CI from −3.8% to +7.4% determined as previously described (4)].

Therefore, one can conclude not only that “no proof of difference” (5) exists favouring $C_{inf}$ vs $E_{inf}$ but, more interestingly, $C_{inf}$ and $E_{inf}$ have an equivalent mortality with an equivalence margin set at ±7.5% [“proof of no difference” (5)].

Based on this information, the administration of piperacillin/tazobactam by $E_{inf}$ in patients with sepsis should be preferred over the administration by $C_{inf}$. Finally, it should be recalled that both dosage regimens are off-label.
References


