Position statement on the use of continuous infusion for piperacillin/tazobactam and meropenem within critical care settings within the UK

The British Infection Association and Intensive Care Society are of the opinion that continuous infusions of piperacillin/tazobactam and meropenem should be strongly considered in critically ill patients with severe infections.

Optimisation of antibiotic usage in relation to route of administration, duration and dosing have the potential to improve outcomes from infection and limit harms. The pharmacokinetic and pharmocodynamic properties of different antibiotics influence how they are administered. For beta-lactam antibiotics, maintaining their concentration above the level required to kill bacteria for as long as possible enhances this bacteriocidal activity[1]. Despite this, beta-lactam antibiotics have traditionally been administered as intermittent doses over a 24-hour period. Evidence accumulated from 17 trials[2], including the very large BLING III trial[3], systematically reviewed by Abdul-Aziz and colleagues[2] now provides convincing evidence of benefit of increased survival at 90 days. However, globally there continues to be variation of practice regarding use of meropenem and piperacillin/tazobactam within critical care units, with some using continuous infusion, others extended infusion times, and some persisting with intermittent short infusions of bolus doses. Reasons for this variation may include uncertainty about the benefit of continuous infusion, or concerns about the practicalities of this approach. The BIA and ICS are of the opinion that continuous infusions of these antibiotics should be strongly considered where possible in critically ill patients with severe infections.

We set out some of the principles and address potential concerns about administration. In addition, we highlight that using infusions should reduce the associated carbon footprint and nursing time compared to intermittent or extended duration administration.

Implementation of this approach[4] requires careful coordination between pharmacy, nursing, intensive care medicine and microbiology teams. We set out below some of the principles that need to be considered.

1. Agreement of the relevant teams and professional groups is required for successful implementation
2. Local protocols are required to ensure practice fits with existing workstreams and guidance on safe intravenous therapy and antimicrobial therapy[5].
3. Key considerations for these protocols include compatibility data, which has been recently reviewed by Nunez-Nunez and colleagues[6] with further principles set out by Barton and colleagues[4]. The NHS injectable medicines guide (MEDUSA https://www.medusaimg.nhs.uk) can provide a useful resource in this area.
4. Drug stability is another consideration, with the UK standard defined by the Pharmaceutical Quality Assurance Committee of the National Health Service as ‘a value of 95–105% of the starting concentration of the active pharmaceutical ingredient’[7]. Stability data for piperacillin/tazobactam and meropenem have been summarised by Barton and colleagues[4], whilst piperacillin/tazobactam is stable for

more than 24 hours[4], meropenem may require several 6, 8 or 12hour infusions to cover the 24 infusion period.

5. Continuous infusions are 'off label' indications and should be managed within the clinical and medicines governance arrangements for such indications at the local site.
6. When initiating continuous infusion in a patient without prior administration, a loading dose equivalent to the standard bolus dose should be administered followed by the immediate initiation of continuous infusion.
7. The dose of continuous infusion should be confirmed with the medical, critical care pharmacy and where appropriate microbiology team. A simple method should be provided for converting total daily dose normally given intermittently to continuous infusions given over a 24-hour period.
8. Venous access needs to be considered; however, these drugs can be given via any secure venous route, including peripheral veins, and need not occupy a central venous catheter lumen.
9. At present this recommendation only relates to meropenem and piperacillin/ tazobactam; while there are theoretical reasons for doing the same with other beta-lactams, there is not yet evidence that it makes a difference in practice.
10. Similarly, clinicians should continue to select antimicrobials in line with local guidance and the principals of antimicrobial stewardship and should not use meropenem and piperacillin/ tazobactam where not otherwise indicated for the purposes of giving agents by continuous infusion.
11. Continuous infusion antibiotics are less costly with regards to nursing time[8] and with similar drug costs and lower use of consumables compared to alternative methods of administration.

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