CLINICAL AND MICROBIOLOGICAL EFFICACY OF CONTINUOUS VERSUS INTERMITTENT APPLICATION OF MEROPENEM IN CRITICALLY ILL PATIENTS: A RANDOMIZED OPEN-LABEL CONTROLLED TRIAL


Study Question: Is a continuous infusion of meropenem as efficacious and safe as bolus dose administration in critically ill patients with severe infection?

Study Description: This was a single center, prospective, randomized, open-label comparative study of 214 patients admitted to an ICU with severe infection. Patients meeting inclusion criteria were randomized to 1 of 2 meropenem regimens: loading dose of 2g followed by 1g over 6 hours continuously (infusion group, CI) or 2g given over 30 minutes every 8 hours (bolus group, B). Primary outcome measures were clinical and microbiological cure. Secondary outcomes included length of mechanical ventilation, ICU and hospital length of stay; ICU and in-hospital mortality, duration of meropenem treatment, total meropenem dose and regimen safety.

Results: Baseline demographics were comparable with no significant differences except a longer ICU length of stay before the start of meropenem in the CI group (9 [5 -16] days vs. 7 [3-11] days; p=0.036). Approximately 50% of patients were on concomitant antimicrobial therapy in the clinically evaluable population. Overall clinical cure and improvement were comparable between groups (81 [83%] CI vs. 81 [75%] B, p=0.18). Overall microbiological success was improved in CI vs. B (87 [90.6%] vs. 80 [78.4%], p=0.020). A statistically significantly shorter ICU length of stay was seen favoring CI. The CI group also had an overall shorter duration of therapy and lower total dose of meropenem. Continuous infusion was independently related to microbiological success (OR=2.977; 95% CI =1.050 to 8.433; p=0.040).

Conclusion(s): A continuous infusion of 4g of meropenem per day had a similar rate of clinical cure as traditional bolus dosing, however, a higher antimicrobial efficacy was achieved as compared to 2g of meropenem given every 8 hours.

Perspective: This study demonstrated comparable clinical cure rates using a CI vs. B dosing therapy, however, better microbiological cure rates did not translate to a better clinical cure rates. Further investigation into the lack of this relationship would be helpful in identifying patients who would most likely benefit from continuous infusions. Future studies assessing the outcomes of CI meropenem in select patient populations is warranted and may prove this dosing strategy superior to traditional dosing.

HIGH-DOSE, EXTENDED-INTERVAL COLISTIN ADMINISTRATION IN CRITICALLY ILL PATIENTS: IS THIS THE RIGHT DOSING STRATEGY? A PRELIMINARY STUDY


Study Question: Is high-dose, extended-interval IV colistimethate (CMS) safe and effective in the critically ill?

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**Study Description:** This was a prospective, observational cohort study in a 16-bed ICU evaluating efficacy (clinical and microbiologic) and nephrotoxicity of CMS in the treatment of critically ill patients with highly resistant gram-negative bacteremia and/or pneumonia. All patients received IV CMS (Colomycin®) 9 MU loading dose then maintenance as follows: 4.5 MU Q12hrs if CrCl >50 mL/min, Q24hrs if CrCl 20-50 mL/min, or Q48hrs if CrCl < 20 mL/min.

**Results:** A total of 28 CMS treatments in 25 patients were included in the analysis. All patients were intubated with a mean APACHE II score of 18±6 and SOFA score of 8±2. Pathogens isolated included *A. baumannii* (46.4%), *K. pneumonia* (46.4%), and *P. aeruginosa* (7.2%). Clinical cure was determined in 82.1% of patients, and of these, microbiologic cure occurred in 73.9% of patients. No significant reduction in renal function was observed in 82.1% of treatment courses. AKI occurred in 5 treatment courses; however none required renal replacement therapy or discontinuation of CMS. Also, serum creatinine (Scr) returned to baseline during follow-up, which took a median of 9.5 days from CMS discontinuation. No correlation was found between Scr and daily or cumulative dose of CMS, as well as Scr and duration of CMS treatment.

**Conclusion(s):** High-dose, extended-interval IV CMS may be effective for the treatment of highly resistant gram-negative infections in the ICU with no significant nephrotoxicity.

**Perspective:** Half of the patients included in this study received CMS as monotherapy. In the remaining half, 69.2% of patients also received an aminoglycoside. However, information regarding the dosing and monitoring of aminoglycosides were not presented in this study. Furthermore, the relatively small patient size limits the ability to accurately describe the risk of nephrotoxicity associated with this CMS dosing regimen. Of note, there are significant differences in the labeling and dose recommendations of CMS in the US compared to Europe. In the US, the dose of CMS (Coly-Mycin M®) is expressed in mg, whereas in Europe the CMS dose is labeled as units (1 mg is approx. 12,500 IU of CMS).

**Magnesium for aneurysmal subarachnoid haemorrhage (MASH-2): A randomized placebo-controlled trial**


**Study Question:** Is there an improved clinical outcome with the use of intravenous magnesium sulfate in patients with aneurysmal subarachnoid haemorrhage?

**Methods:** This was a three phase randomized, multi-center, placebo-controlled trial. Adult patients admitted to a neurological or neurosurgical ICU within 4 days of haemorrhage and a diagnosis of aneurysmal subarachnoid haemorrhage were included. Patients were randomized to magnesium sulfate therapy or placebo (blinded) by a computer generated code. Those receiving magnesium sulfate therapy were administered a regimen of 64 mMol/day IV over 24 hours for 20 days after haemorrhage onset, until hospital discharge, or death, whichever occurred sooner. Local treatment protocols were used which included nimodipine 360 mg/day, aneurysm occlusion, bed rest, and normovolemia. The primary outcome was dependence (defined as Rankin Scale score of 4 or 5) or death, 3 months after haemorrhage.
Results: A total of 1204 patients were enrolled and randomized to magnesium (n=606) or placebo (n=597). Baseline data did not differ between the groups. Results showed no significant difference in the primary outcome, symptoms or mRankin Scale score between groups.

Conclusion: Based on the results of this trial, authors recommend against the routine use of IV magnesium (64 mMol/day) to prevent delayed cerebral ischemia following aneurysmal subarachnoid haemorrhage, due to lack of beneficial outcome.

Perspective: Magnesium has mechanisms of neuroprotection that are thought to help prevent delayed cerebral ischemia. However, as the authors note in discussion, this effect may not be adequate enough to overcome other complications of aneurysmal subarachnoid haemorrhage that play a role in outcome. Results of this study are consistent with other trial data that IV magnesium sulfate does not affect outcome after aneurysmal subarachnoid haemorrhage.

PROCALCITONIN USEFULNESS FOR THE INITIATION OF ANTIBIOTIC TREATMENT IN INTENSIVE CARE UNIT PATIENTS


Study Question: Does a procalcitonin guided strategy (PCT) for the decision to treat infection reduce antibiotic consumption?

Methods: This is a single-center, randomized, prospective study from April-Dec 2008. Patients > 18 years of age and hospitalized > 2 days in an ICU were randomized to PCT or control (physician was blinded to PCT result. The primary endpoint was the difference in antibiotic consumption between groups. Secondary endpoints included: usefulness of PCT in ICU diagnostic algorithms and determination of concordance of infection diagnostic ratings by the ICU physician and an ID specialist blinded to PCT results.

Results: There were 509 patients eligible for the study with no statistically significant differences in baseline characteristics. Neither antibiotic consumption between PCT and control, nor median defined daily dose (DDD)/100 ICU days differed significantly between groups. No difference in the decision to treat by PCT result was found among the groups.

Conclusions: Using a PCT to determine appropriateness of initiation of antibiotics did not lower antibiotic consumption, nor did it improve the accuracy of diagnosis by ICU clinicians.

Perspective: This study suggests that PCT is not a reliable marker of infection, however they did not use serial PCT throughout antibiotic course to guide decision-making, which has been suggested to reduce consumption in other studies. The benefit and cost-effectiveness of this approach requires further study in a multi-center design.
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