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CONTINUOUS ANTIBIOTIC INFUSIONS

Evidence Based Medicine Guideline

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Approved: 5/15/2007 Revision(s): 7/2/2023

SUMMARY
It is well established that β-lactam and glycopeptide antibiotics exhibit time dependent killing. The degree of antimicrobial killing correlates well with the amount of free drug remaining above the minimum inhibitory concentration (MIC) for a given amount of time over the dosing interval. Continuous infusion is a method of administration that allows for consistent steady state concentrations and maximizes the percent of time above an organism's MIC. Continuous infusion is an alternative to intermittent infusion. It does not demonstrate an economic, clinical, or microbiologic benefit to current standard of practice, but may have clinical value in specific patient situations.

RECOMMENDATIONS

- **Level 1**
  - **Continuous infusion of piperacillin/tazobactam or vancomycin is a safe and effective alternative to intermittent infusion for the treatment of appropriate infections.**
- **Level 2**
  - **Continuous infusion of Cefazolin is a safe and effective alternative to intermittent infusion for the treatment of appropriate infections.**
- **Level 3**
  - **Continuous infusion piperacillin/tazobactam should be considered for infections due to multi-drug resistant organisms when sensitivities to piperacillin/tazobactam are reported as "Intermediate."**
  - **No recommendation can be made regarding the administration of meropenem as a continuous infusion.**
  - **There is insufficient evidence to support the use of cefepime administered as a continuous infusion.**

INTRODUCTION

Continuous infusion of antimicrobial agents has been studied since the 1950s. Penicillin was the first antibiotic studied using this method of administration. Investigators noted that it was most effective when serum concentrations at the site of infection remained above those that were necessary to kill the bacteria. In order to achieve maximal efficacy, penicillin had to be administered by continuous infusion or at 2-4 hour intervals. This early observation provided a basis for the concept of time-dependent killing. More recently, studies have provided evidence that the time-dependent activity of beta-lactam antibiotics is dependent on the percentage of time above the bacteria's MIC and correlates well with therapeutic efficacy (1). Greater killing is not achieved with beta-lactam antibiotics once the MIC is exceeded by 4-5 times. The results of clinical trials have established the minimum percent time above the MIC for many beta-lactam agents. Optimal efficacy of penicillins, cephalosporins, and carbapenems is achieved when serum concentrations remain above the MIC for ≥ 50%, 50-60%, and 20-40% of the dosing interval, respectively (2-4).

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

Augmented Renal Clearance (ARC)

Augmented renal clearance is a phenomenon that has been described in critically ill patients and is characterized by a creatinine clearance (CrCl) >130 mL/min. Neurologically injured and burn patients are at higher risk due to hemodynamic alterations, aggressive fluid resuscitation, vasopressor usage, osmotherapy agents, and increased cardiac output from the sympathetic nervous system responses to illness. ARC may result in suboptimal concentrations of antibiotics that exhibit time-dependent killing, leading to treatment failure. Two major scoring systems have been developed to predict the likelihood of ARC, the ARC score and the ARCTIC (ARC in trauma intensive care) score (5). Udy and colleagues aimed to determine the prevalence of ARC and characteristics to help identify these patients. The authors conducted a prospective, observational study in consecutive traumatized and septic critically ill patients. Age less than 50 years, trauma, and a modified sequential organ failure assessment (SOFA) score <4 were found to be significant risk factors for enhanced renal elimination (6). Akers and colleagues utilized pharmacokinetic data from trauma/surgical intensive care unit patients who received piperacillin/tazobactam. They found the ARC score to be 100% sensitive and 71.4% specific for detecting increased clearance, increased volume of distribution, decreased area under the curve, and achievement of free concentrations greater than a minimum inhibitory concentration (MIC) of 16 µg/mL for at least 50% of the dose interval (fT > MIC ≥ 50%) (7). Barletta and colleagues conducted a retrospective cohort study to evaluate the incidence of ARC, identify ARC risk factors, and describe a model to predict ARC in trauma patients. The incidence was found to be 67% with a mean CrCl of 168 mL/min. Multivariate analysis revealed the following risk factors for ARC: age <56, age 56-75, serum creatinine less than 0.7 mg/dL, and male sex. An ARCTIC score of 6 or higher was found to have a positive predictive value of 0.842 and a negative predictive value of 0.682 (8).

	ARC Scoring System	ARCTIC Scoring System
Criteria	Age < 50 years: 6 points Trauma: 3 points SOFA ≤4: 1 point	Serum creatinine <0.7 mmol/L: 3 points Sex: male: 2 points Age <56 years: 4 points Age 56-75 years: 3 points
Interpretation	0-6 points: low risk 7-10 points: high risk	<6 points: low risk ≥6 points: high risk

LITERATURE REVIEW

Piperacillin/tazobactam

Lau and colleagues conducted a non-inferiority study comparing the safety and efficacy of continuous versus intermittent infusion of piperacillin/tazobactam in patients with complicated intraabdominal infections. Those with severe renal dysfunction [creatinine clearance (CrCl) <20 mL/min], necrotizing pancreatitis, irreversible shock, and neutropenia were excluded. Two hundred sixty-two patients from 33 sites were randomized. Duration of therapy ranged from 4-14 days. There were no differences between groups in the rate of clinical success at the test of cure visit 10-21 days after the last dose. Continuous infusion was well tolerated and displayed a safety profile similar to that of intermittent infusion (9). (Class I)

Grant and colleagues performed a prospective, open-label study of continuous versus intermittent administration of piperacillin/tazobactam evaluating clinical, microbiologic, and economic outcomes. Patients with an absolute neutrophil count <1000 cells/mm^3 and severe renal dysfunction (CrCl < 20 mL/min) were excluded. Ninety-eight patients with clinical signs and symptoms consistent with infection were enrolled. There were no differences in clinical or microbiologic outcomes. However, the total amount of antibiotic administered per day was decreased by one-third and the mean cost for patients treated successfully with continuous infusion was statistically significant (p=0.008). No adverse events were directly associated with either regimen. Continuous infusion provided clinical and microbiological outcomes that resembled that of intermittent infusion but was more cost-effective (1). (Class II)

Burgess and colleagues evaluated the pharmacokinetics and pharmacodynamics of piperacillin/tazobactam administered by continuous or intermittent infusion in a prospective, randomized, crossover study. Five clinical isolates each of *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* were used for pharmacodynamic analyses. Patients with a history of drug or alcohol abuse, chronic disease, or a CrCl ≤ 80 mL/min were excluded. Eleven healthy volunteers were admitted on three separate occasions with a ≥ 7-day washout period. During each admission, patients were randomized to one of three dosing regimens. The 13.5 gm continuous infusion regimen consistently resulted in higher concentrations above the breakpoint for *K. pneumoniae* and many of the susceptible strains of *P. aeruginosa* than did the 6.75g continuous infusion (10). (Class II)

Vancomycin

In a multicenter, prospective, randomized study, the administration of vancomycin by continuous or intermittent infusion in ICU patients with severe methicillin-resistant *Staphylococcus aureus* (MRSA) infections was compared in order to determine efficacy, safety, and cost-effectiveness. Patients with more than three organ failures, neutrophil cell count <1,000 cells/mm^3, or a serum creatinine <2.3 mg/dL were excluded. One hundred nineteen patients with direct microbiologic examination showing gram-positive cocci were enrolled. There was no significant difference between treatment failures at treatment end between groups. However, targeted trough concentrations were achieved faster (p=0.03), there was less variability between the groups with respect to AUC_{24} (p=0.026) and fewer samples per treatment were obtained in the continuous infusion group (p<0.0001). Overall cost was 23% lower in the continuous infusion group. However, when the mean ± standard deviation of cost is taken into account, the results would suggest there is no difference between treatment groups. Nevertheless, continuous and intermittent infusions remain comparable in clinical efficacy and safety (11). (Class I)

Meropenem

In a double blind, international, RCT (2023 MERCY trial), Monti and colleagues sought to determine whether continuous versus intermittent infusion of Meropenem reduces all-cause mortality and emergence of pan-drug or extensively drug resistant bacteria. The study was conducted across 31 ICUs in 26 hospitals in 4 different countries. Eligible patients included those ≥18 years old admitted to the ICU with sepsis or septic shock requiring new antibiotic treatment with meropenem. Patients with low probability of survival, severe immunosuppression or previous carbapenem treatment were excluded. The study was conducted from June 2018-August 2022 and final 90-day follow-up was completed in November 2022. The study included 607 participants and primary outcomes were measured at 28 days and a 90-day mortality follow-up was completed. The primary outcome was a composite of all cause mortality as well as emergence of pan-resistant or extensively resistant bacteria. Secondary outcomes included days alive and free from antibiotics at day 28, days alive and free from the intensive care unit at day 28, and all-cause mortality at day 90. At 28 days and 90 days there was no statistically significant difference in the primary or secondary outcomes. The results of the MERCY trial suggest that continuous administration of meropenem offers no improvement in clinical outcomes ICU patients with sepsis and septic shock (12). (Class I).

In 2018, Yu and colleagues completed a systematic review and meta-analysis of prolonged (extended or continuous) vs. intermittent infusion of meropenem for the treatment of severe infection. Two independent reviewers completed literature searches using Medline, EMBASE, and Cochrane database, The review included relevant publications between 2012 and October 2017. A total of ten studies were included (6 RCTs and 4 observational studies). A modified Jadad scale was used to evaluate the quality of included studies and those included were determined to be high quality. The included studies involved a total of 951 patients with sample sizes ranging from 30-214 patients. Outcomes investigated included mortality, clinical cure rate, microbiological eradication, and adverse events. The analysis concluded that evidence from the included studies suggest continuous infusion of meropenem could lead to lower mortality and higher clinical improvement (13). (Class II)

The BLING III trial is currently underway with an estimated completion date of 2023. This is a phase III multi-center RCT which aims to determine whether a continuous infusion of beta-lactam (piperacillin-tazobactam or meropenem) results in decreased all cause 90-day mortality compared with intermittent dosing. It includes roughly 7,000 patients from 70 ICUs worldwide and when complete will be the largest trial to date investigating continuous vs. intermittent dosing (14).

Cefepime

Bauer and colleagues retrospectively evaluated the clinical and financial outcomes of continuous versus intermittent infusion of Cefepime in patients with respiratory or blood cultures positive for gram negative bacteria. A subgroup analysis of those with Pseudomonas Aeruginosa was also conducted. Eligible patients were ≥18 years old, had a discharge diagnosis of pneumonia or bacteremia, had cultures susceptible to cefepime, received cefepime with 72 hours of the onset of infection and received cefepime for ≥48 days. Patients who were incarcerated, receiving concurrent Beta lactam anti-biotics, or receiving both continuous and intermittent cefepime were excluded. Outcomes investigated included days on mechanical ventilation, hospital and ICU LOS, and hospital mortality. Financial impacts were assessed by comparing hospital costs incurred during cefepime administration and adjusted for inflation. A total of 592 patients were included in the study (202 received extended infusion, 390 received intermittent infusion). No significant differences were found in LOS, cost of stay or mortality. A total of 87 patients were included in the P. Aeruginosa subgroup analysis. Hospital and ICU LOS, hospital costs, days on mechanical ventilation and overall mortality were lower in the group receiving extended infusion (15) (Class III).

Currently there are no prospective randomized control trials investigating the clinical effectiveness of continuous verses intermittent infusion of cefepime.

Cefazolin

Shoulders and colleagues retrospectively evaluated the clinical efficacy and safety of intraoperative continuous versus intermittent cefazolin dosing. This study included adult patients who underwent coronary artery bypass grafting on cardiopulmonary bypass. Patients in the continuous infusion group received a loading dose of cefazolin based on their weight followed by a continuous infusion dependent on renal function. Patients in the intermittent group received intermittent dosing dependent on weight given every two hours during surgery. Both patients received intermittent dosing for 24 hours after chest closure adjusted based on weight and renal dysfunction. The primary outcome of incidence of surgical site infections (SSIs) was lower in the continuous infusion group compared to the intermittent dosing group (4.6% in the INT cohort vs 1.7% in the CI cohort, p=0.116). Superficial surgical site infections were significantly lower in the continuous infusion group (2.8% in the intermittent group vs 0.4% in the continuous infusion group, p=0.039). In addition, the safety analysis found that although patients in the continuous infusion group received higher cumulative doses, there was no significant difference between groups in the incidence of seizures, acute kidney injury, or need for postoperative dialysis. Although this study did not reach statistical significance for the primary outcome, it does show the efficacy and safety of continuous infusion cefazolin dosing (16). (Class 2).

ADMINISTRATION RECOMMENDATIONS

Duration of therapy between continuous and intermittent infusion was not evaluated in the above studies. Therapy should, therefore, continue until signs and symptoms of infection resolve and should be discontinued at the physician's discretion. Continuous infusion antibiotics should be administered via a dedicated line. If access is limited, stop the continuous infusion, flush the line, administer the needed medication, flush the line again, and then resume the continuous infusion.

Dosing Recommendations

Piperacillin/tazobactam

	Serious infections, critically ill or morbid obesity (e.g.BMI≥40)	Moderate infections in non-critically ill, non-obese patients
Loading Dose:	4.5 g IV x 1 over 15 min	
Infusion Rate:		
CrCl >20 mL/min	18g IV over 24 hours	13.5 g IV over 24 hours (9 mL/hr)
CrCl <20 mL/min	9 g IV over 24 hours	Not recommended

Special considerations

- Piperacillin/tazobactam is incompatible with many medications including acyclovir, amphotericin B, famotidine, gentamicin, haloperidol, tobramycin, and vancomycin.
- Continuous infusion of piperacillin/tazobactam can be stopped for up to four hours without the need for re-bolusing. If necessary, a loading dose of 4.5 g IV x 1 over 15 minutes should be administered followed by resumption of the continuous infusion.

Pharmacy considerations

- To limit wastage, all doses will be supplied as 4.5 g bags to run continuously
    - 18.5 g daily: 4.5 g CI over 6 hours (4 bags per day)
    - 13.5 g daily: 4.5 g CI over 8 hours (3 bags per day)
    - 9 g daily: 4.5 g CI over 12 hours (2 bags per day)

Vancomycin

Loading Dose:	25 mg/kg x 1
	Infusion Rate:
ICU patients with augmented renal clearance	50-60 mg/kg/day over 24 hours Consider 40-50 mg/kg/day for older/obese patients
Healthcare associated CNS infections	50-60 mg/kg/day over 24 hours Consider 60 mg/kg/day for age <30 Consider 50 mg/kg/day for CrCl 50-90 mL/min Consider 40-50 mg/kg/day for older or obese patients Not recommended if CrCl < 50 mL/min
CRRT (when used as an alternative to pulse dosing)	15-20 mg/kg/day over 24 hours Consider starting obese patients at 15 mg/kg/day

Special considerations

- Adjust total daily dose in 500 mg increments.
- Measure trough concentration every 24 hours until two consecutive levels are obtained within the desired range.

Meropenem

Loading Dose:	500 mg x 1 over 30 minutes
Infusion Rate: CrCl $\geq$ 50 mL/min CrCl 30-49 mL/min CrCl < 30 mL/min	 6 g over 24 hours (8 g dosing is reserved for patients with subtherapeutic levels on 6g) 4 g over 24 hours Not recommended

Stability Considerations:

- Due to stability, all doses supplied as 1 or 2 g bags to run continuously.
    - 8 g daily: 2 g CI over 6 hr (4 bags per day)
    - 6 g daily: 2 g CI over 8 hr (3 bags per day)
    - 4 g daily: 1 g CI over 6 hr (4 bags per day)

Cefepime

Loading Dose:	1 g x 1 over 30 minutes
Infusion Rate: CrCl $\geq$ 30 mL/min CrCl 10-29 mL/min CrCl <10 mL/min	 6 g over 24 hours 8 g dosing is reserved for patients with subtherapeutic levels on 6g) 4 g over 24 hours Not recommended

Pharmacy Considerations:

- To limit wastage, all doses will be supplied as 2 g bags to run continuously
    - 8 g daily: 2 g CI over 6 hours (4 bags per day)
    - 6 g daily: 2 g CI over 8 hours (3 bags per day)
    - 4 g daily: 2 g CI over 12 hours (2 bags per day)

Cefazolin

Loading Dose:	1 g x 1 over 30 minutes
Infusion Rate: CrCl ≥ 30 mL/min CrCl 10-29 mL/min CrCl <10 mL/min	 6 g over 24 hours (8 g dosing is reserved for patients with subtherapeutic levels on 6g) 4 g over 24 hours Not recommended

Pharmacy Considerations:

- To limit wastage, all doses will be supplied as 2 g bags to run continuously
    - 8 g daily: 2 g CI over 6 hours (4 bags per day)
    - 6 g daily: 2 g CI over 8 hours (3 bags per day)
    - 4 g daily: 2 g CI over 12 hours (2 bags per day)

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