## Case Report

## Amoxicillin-clavulanate dosing in the ICU: the additive effect of renal replacement therapy in a patient with normal kidney function

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## Abstract

Dosing of amoxicillin-clavulanic acid in critical illness is difficult as beta-lactam pharmacokinetics are altered by physiological changes and therapies initiated in the intensive care unit such as renal replacement therapy (RRT). Successful treatment relies on sustaining a free antibiotic concentration above the minimum inhibitory concentration of the target pathogen (fT>MIC). We present a case of a patient treated with amoxicillin-clavulanic acid (1.2g 8-hourly) for an aspiration pneumonia. Dosing in this case was complicated by the necessity for RRT to treat a drug overdose with carbamazepine, despite normal native renal function. Antibiotic concentrations taken at steady state revealed a clearance of 14.6L/hr and a low *f*T>MIC (<40%). Analysis of urine drug concentration suggested 48% of clearance was via the native kidneys. This case illustrates that careful consideration of antibiotic dose and frequency is required in critically ill patients receiving renal replacement therapy and highlights the need for further research in this patient group. In future similar cases, we would consider a dose of 2.2g 6- or 8-hourly with early therapeutic drug monitoring.

## Introduction

The broad-spectrum antibiotic amoxicillin-clavulanic acid is a common choice for the treatment of various infection syndromes in the intensive care unit. The choice of dose and frequency of administration for amoxicillin-clavulanic acid is difficult for patients who are also receiving renal replacement therapy (RRT) as it has significant renal elimination and is cleared by haemodialysis and haemofiltration (1-3). Clearance will be particularly high in cases where RRT is used when native renal function is normal, for example where RRT is used to clear toxins in drug overdose. Observational data suggests that sub-optimal antibiotic exposure is associated with treatment failure in the intensive care unit (4). Successful treatment with beta-lactams like amoxicillin relies on sustaining free antibiotic concentrations above the minimum inhibitory concentration of the target pathogen (*f*T>MIC) (5). Despite this knowledge, a recent systematic review of amoxicillin-clavulanic acid pharmacokinetics identified no studies in critically ill patients receiving continuous renal replacement therapy (6). We present a case report of the pharmacokinetics of amoxicillin in a patient with preserved renal function receiving continuous veno-venous hemodiafiltration (CVVHDF) following a drug overdose.

## Case report

### History and management

A 44-year-old man (height 180 cm, weight 120 kg) presented to the emergency department following a polypharmacy overdose. Drugs consumed included 28 g carbamazepine, 150 mg of diazepam and an unknown quantity of alcohol. He was intubated for airway protection in the setting of a low level of consciousness and transferred to the intensive care unit where CVVHDF was commenced to facilitate clearance of carbamazepine. Native renal function was normal with a serum creatinine of 68 μmol/L prior to commencement of CVVHDF.

On day 2 of his admission amoxicillin-clavulanic acid (1.2g 8-hourly) was commenced to treat aspiration pneumonia. Amoxicillin concentrations were measured on day 4 of therapy to assess adequacy of treatment. CVVHDF was ongoing at an effluent dose of 34 mL/kg/hr (ultrafiltration dose 20 mL/kg/hr, pre-dilution 1800 mL/hr). Consent for sampling was obtained from the patient’s legally authorised representative with approval also granted by the local research ethics committee.

*Staphylococcus aureus* and *Klebsiella pneumoniae* were subsequently isolated from sputum and both pathogens were reported as susceptible to amoxicillin-clavulanic acid (Vitek, BioMérieux, FRA). There was no change in antibiotic therapy at this stage as there was clinical improvement. Antibiotics and CVVHDF were continued until day 8 of admission (5-day course of antibiotics). He was extubated on day 9 with resolution of the pneumonia and neurological recovery. He was discharged from hospital 10-days later.

### Amoxicillin pharmacokinetics

Unbound amoxicillin concentrations were separated using a validated ultrafiltration method with an Amicon Ultra 0.5ml 30,000-molecular-weight-cutoff centrifugal filter device (Merck Millipore, Sydney, AUS). Amoxicillin serum concentrations were quantified using a validated Ultra Performance Liquid chromatography (UPLC) coupled with QDa mass detection (Waters Corporation, Milford, MA, USA). The lower limit of quantification (LLOQ) was 0.1 mg/L, linearity up to 50 mg/L and the inter-run imprecision was < 10% across 3 quality control levels.

The free (unbound) amoxicillin concentration profiles from serum, dialysis effluent and urine are shown in Table 1. The trough concentration was 1 mg/L and area under the curve for the dosing interval (AUC0-8, trapezoid method) in plasma was 48.1 mg.hr/L.

Pharmacokinetic parameters were estimated using NONMEM version 7.3 (ICON plc) (7). Other data interpretation was undertaken using R language and environment for statistical computing (8). Total amoxicillin clearance was 14.6 L/hr and volume of distribution was 30.9 L.

The mean saturation coefficient for the CVVHDF was 0.96 (calculated as amoxicillin concentration in effluent / pre-filter amoxicillin concentration in plasma). This gives a CVVHDF clearance of 3.2 L/hr (9). Comparing drug amount in plasma and urine (scaling concentrations by volume of distribution and urine volume) gives an AUC of 1486 mg.hr and 718 mg.hr respectively. This suggests 48% of plasma clearance was via native renal function.

## Discussion

This case highlights the challenges of dosing in a patient with preserved kidney function and receiving CVVHDF, where a typical renally cleared drug would have two clearance routes. In the present scenario, an appropriate empirical (beforea pathogen has been identified) MIC target for amoxicillin would be 8 mg/L (10, 11). This target is derived from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoint for Gram negative organisms (12). Free antibiotic concentrations were below this target early in the dosing interval (<40% *f*T>MIC, extrapolated from serum concentrations at 2 and 4 hours). Consensus is lacking on the optimal target *f*T>MIC for beta-lactams in severe infection. Most argue it should be over 50% of the dosing interval, with some arguing it should be >4\*MIC for the whole dosing interval (4). This suggests 8-hourly dosing in this case may have provided sub-optimal antibiotic concentrations for a pathogen with an MIC close to the clinical breakpoint MIC. In addition to CVVHDF, preserved native renal function and large body mass will have contributed to the low serum concentration profile for this patient.

For the majority of infections treated in intensive care, the true pathogen MIC is often unknown until late in the treatment course, if at all. We therefore argue that the ideal concentration profile for amoxicillin-clavulanate would target a worst-case scenario – one in which the true MIC is equal to the clinical breakpoint MIC (i.e. the highest MIC considered susceptible to treatment). This argument is in keeping with the wider antimicrobial pharmacokinetic literature (4, 13, 14). In this case, both pathogens (*Staphylococcus aureus* and *Klebsiella*) were reported as sensitive to amoxicillin-clavulanate. Our laboratory does not routinely report MIC values of isolated pathogens. It is possible that the true MIC of these pathogens was lower than the clinical breakpoint MIC of 8mg/L. This is perhaps reflected in the clinical improvement in this case despite a pharmacokinetic profile that is sub-optimal for the worst-case (8mg/L) MIC scenario for an amoxicillin-clavulanate susceptible organism.

There is no consensus in cases such as this as to the choice of dose and frequency of amoxicillin-clavulanic acid. This reflects a lack of published pharmacokinetic data. To our knowledge, there is only one previously published pharmacokinetic study and model of amoxicillin-clavulanic acid in critical illness, by Carlier al. (13). The 6-hourly dosing used in this case is in keeping with recommendations from this work, but while this dosing interval is common across Europe and Australia, it is not universal. For example, the British National Formulary recommends a dose of 1.2g IV every 8 hours (15). The Carlier study did not include anyone receiving RRT and the only empirical data on amoxicillin clearance during RRT derives from small studies in the 1970’s and 80’s in patients with end stage chronic kidney disease who were receiving intermittent haemodialysis (1, 2, 16) and a small study by Bouman et al. of critically ill patients receiving continues RRT (haemofiltration) (3). Unfortunately, these data are insufficient to guide dosing adjustments for continuous dialysis and filtration techniques. Choice of RRT modality (haemofiltration, haemodialysis, low-efficiency), blood and effluent flow rates and filter type will all effect drug clearance. For example, in the Bouman study (haemofiltration alone), mean CRRT clearance of amoxicillin was approximately 10% lower than that measured in this patient (haemodiafiltration), 2.9 versus 3.2 L/hr respectively. In addition, many patients retain some native renal function and non-renal elimination routes may be normal or up-regulated (17). The high urinary output of amoxicillin found in this case despite low urine output (table 1) highlights the limited utility of urine output as a surrogate for native renal function. It is also worth noting that drug doses are commonly reduced when RRT is instigated.

Clavulanic acid concentrations were not measured in this case as there is no local assay, a not uncommon situation globally. Whilst this is a limitation, our intention in publishing this case is to highlight the potential for under-dosing and we would argue that dose adjustment will largely be related to amoxicillin.

## Conclusion

This case demonstrates that patients with preserved renal function receiving RRT for drug toxicity may require dose increases of prescribed medicines to ensure that therapeutic concentrations are achieved. Further research is clearly needed and should include a pharmacokinetic study of both amoxicillin and clavulanic acid in critically ill patients receiving renal replacement therapy.

In future similar cases, we would consider a dose increase to 2.2g 8- or 6-hourly with early therapeutic drug monitoring. Although this advice should be viewed as cautious expert opinion rather than a robust evidence-based recommendation.

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### Statement of ethics

Written consent was obtained from the patient’s legally authorised representative with approval granted by the local research ethics committee.

### Disclosure Statement

Professor Lipman has received grants and honoraria from MSD. Professor Roberts reports personal fees from Astellas, personal fees from Biomerieux, personal fees from Accelerate Diagnostics, other from Bayer, grants from MSD, grants from Cardeas, grants from The Medicines Company, outside the submitted work. DL has no conflict of interest to declare.

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### Author contribution

All authors contributed to the draft manuscript and data analysis.

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