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O0808 Standard beta-lactam doses fail to achieve PK/PD targets in critically ill patients of all ages, with children particularly at risk: results from the ABDose study

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Background: There is a growing body of evidence from critically-ill adults that standard doses of beta-lactams fail to achieve pharmacokinetic/pharmacodynamic (PK/PD) targets associated with successful treatment(1). Data is lacking for many antibiotics in children and neonates. We aimed to describe antibiotic PK and PK/PD target attainment in an age inclusive study (ABDose) of beta-lactams in critically-ill adults, children and neonates.

Materials/methods: Study participants were adults, children and neonates admitted to intensive care and receiving one or more of eight beta-lactams as part of standard treatment. Following informed consent or assent, blood samples were obtained at predefined time-points between doses. Plasma was frozen at -80°C and concentrations were measured retrospectively using ultra-high-performance liquid chromatography tandem mass spectrometry. Population-PK modelling was undertaken using non-linear mixed-effects modelling software (NONMEM v7.3, Icon plc). Minimum PK/PD targets of time with free concentration above the minimum inhibitory concentration (MIC) of the target pathogen (fT>MIC) at 50% and 100% of the dosing interval were used, alongside more conservative targets of concentration >4xMIC(1). Ethical approval was provided by the national research ethics committee, London (14/LO/1999).

Results: 216 participants (144 adults, 51 children, 21 neonates) provided 1283 samples for analysis. Allometric scaling and organ maturation functions were used to produce age inclusive pharmacokinetic models for each drug. The range of doses received by adults was greater than children and neonates, e.g. benzylpenicillin 10–34mg/kg adults vs 47–55mg/kg neonates (median 17mg/kg vs 50mg/kg). Only 73% of antibiotic courses achieved 50%*f*T>MIC. There was marked heterogeneity in the %fT>MIC in adults (Figure 1). Paediatric participants were significantly less likely to achieve the lowest PK/PD target compared to adults (49% vs 74% achieving 50%*f*T>MIC, $p<0.01$ Chi-squared).

Conclusions: Current dosing regimens fail to achieve recognised PK/PD targets for a large proportion of critically ill patients. Children appear particularly vulnerable to under-dosing. The standard, “one size fits all” dosing in adults contributes to a failure to achieve PK/PD targets. To our knowledge, ABDose is the first study to demonstrate that antibiotic PK data from adults, children and neonates can be modelled simultaneously by using scaling and maturation functions.

Roberts *et al.*(2014).*Clinical Infectious Diseases***5(8):**1072-1083

Figure 1. Percentage of time with free serum concentration above bacterial minimum inhibitory concentration (%fT>MIC) for participants in the ABDose study, separated by drug and clinical setting (adult, paediatric and neonatal intensive care)