EV0016

Lack of PK/PD target attainment in de-escalated antibiotic therapy in critically ill patients: less is not always more

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Background

Although de-escalation of antibiotic therapy is a key element in many antibiotic stewardship programs, the possible change in pharmacokinetic/pharmacodynamic (PK/PD) target attainment in de-escalation has not yet been considered. A recent study found that de-escalation did not reduce intensive care unit (ICU) length of stay and actually increased use of antibiotics in patients who had been de-escalated. Based on this, we hypothesized that PK/PD target attainment after de-escalation may be lower than with empiric therapy, even when the pathogen is reported to be susceptible to the de-escalation antibiotic.

Objectives

1) To compare the probability to achieve a therapeutic exposure of contemporary dosing of empirical broad-spectrum ß-lactam antibiotics and narrower spectrum antibiotics for a number of pathogens for which de-escalation may be considered
2) To determine whether this could be improved with alternative dosing strategies

Materials and methods

• We performed a simulation study using published population pharmacokinetic models in critically ill patients

• 1000 Monte Carlo simulations were undertaken for each antibiotic and each dosing regimen using a dataset obtained from critically ill patients with sepsis without renal failure (n=49), collected as part of another study. The patient characteristics are shown in table 1.

• The antibiotics and the simulated dosages are shown in table 2.

  • Broad-spectrum ß-lactam antibiotics : meropenem and piperacillin

  • Narrower spectrum antibiotics : amoxicillin, cefuroxime and flucloxacillin

Table 1 : Patient characteristics of the simulated dataset

Characteristic	Median (IQR)
Male / female (N)	27/22
Age (years)	46 (33-64)
Height (m)	1.70 (1.63-1.80)
Weight (kg)	84 (73-95)
BMI (kg/m²)	29.4 (25.1-33.3)
Creatinine clearance (mL/min)	105 (74-143)
APACHE II score	17 (14-25)
SOFA score	6 (5-9)
Serum urea concentration (mmol/L)	6.2 (3.9-8.7)
Serum creatinine concentration (µmol/L)	73 (55-97)
Serum albumin concentration (g/L)	21 (20-24)
8 hour creatinine clearance (mL/min)	112 (76-142)
Mechanically ventilated (%)	93.4

Table 2 : Simulated dosages and mode of administration

Antibiotic	Dosage simulation
Meropenem	1 g every 8 h as an intermittent infusion 1 g every 8 h as a 4h extended infusion 3 g/day as a continuous infusion
Piperacillin	4 g every 8 h as an intermittent infusion 4 g every 8 h as a 4h extended infusion 12 g/day as a continuous infusion 4 g every 6 h as an intermittent infusion 4 g every 6 h as a 3h extended infusion 16 g/day as a continuous infusion
Amoxicillin	1 g every 6 h as an intermittent infusion
Cefuroxime	1.5 g every 8 h as an intermittent infusion
Flucloxacillin	1 g every 6 h as an intermittent infusion

•The time for which the free antibiotic concentration exceeds the minimal inhibitory concentration ($fT_{>MIC}$) was calculated for each subject.

•PK/PD target : 40% $fT_{>MIC}$ for carbapenems, 50% $fT_{>MIC}$ for penicillins, and 65% $fT_{>MIC}$ for cephalosporins.

•MIC data were obtained from EUCAST to determine the probability to achieve a therapeutic exposure, which was described as a fractional target attainment (FTA). This is a clinically relevant descriptor of the likely appropriateness of antibiotic dosing that compares the achievement of the PK/PD target against an MIC distribution. The microorganisms used in this simulation study were microorganisms for which de-escalation is commonly performed: *Escherichia coli, Oxacillin susceptible Staphylococcus aureus, Streptococcus* spp., *Klebsiella pneumoniae, Haemofilius influenzae, Citrobacter freudnii, Morganella morganii* and *Proteus mirabilis*.

Results

Fig 1 shows the probability to achieve a therapeutic exposure (or FTA) for the different antibiotics in contemporary dosing → The FTA for the broad-spectrum antibiotics was higher than for the narrower spectrum antibiotics

The FTA for the higher dosages/ alternative modes of administration are shown in Fig 2 → changing the intermittent infusion to a higher dose continuous infusion improves the FTA dramatically for the narrower spectrum antibiotics.

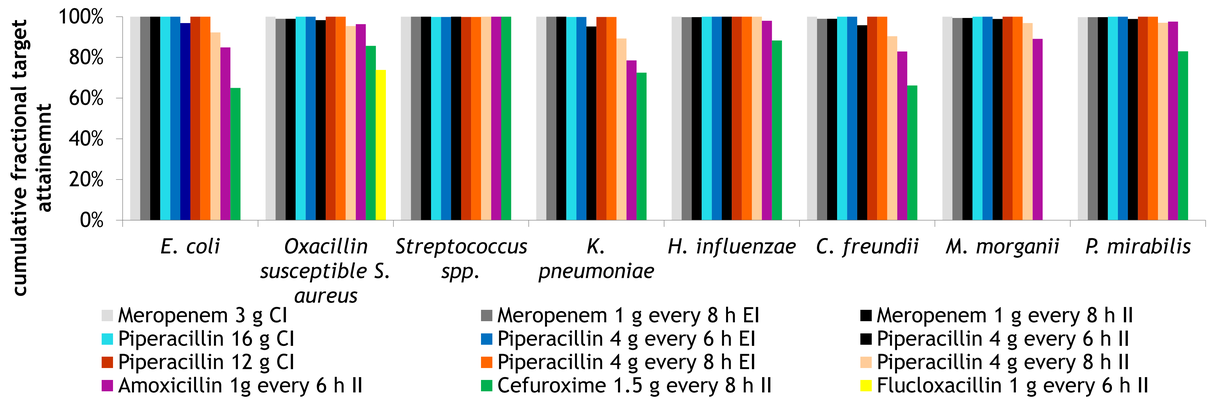

Fig 1: Fractional target attainment for different antibiotics for different microorganisms. CI: continuous infusion, EI: extended infusion, II: intermittent infusion.

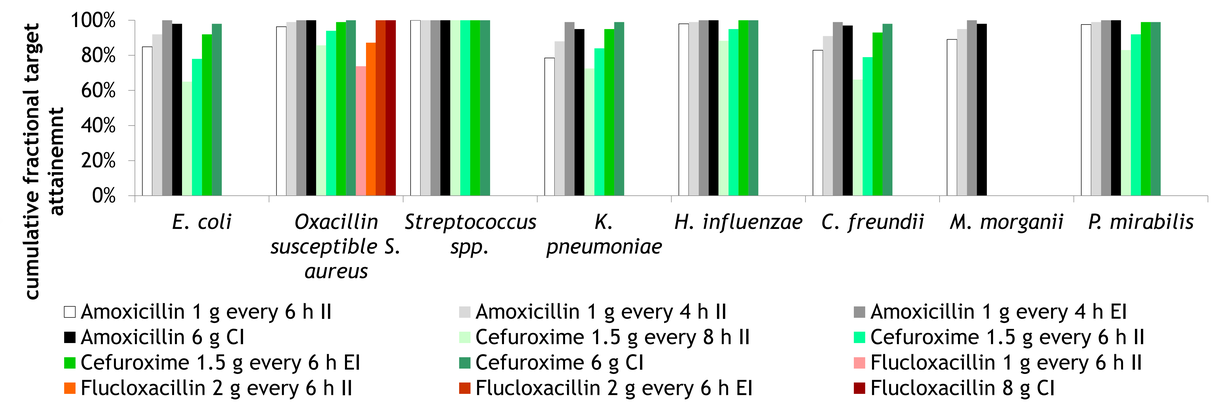

Fig 2: Fractional target attainment for the narrower spectrum antibiotics for different dosages and modes of administration. CI: continuous infusion ; EI: extended infusion ; II: intermittent infusion.

Limitations

• These results are not based on measured concentrations from real patients

• The simulated patient population were patients who had normal renal function and did not include patients with acute kidney injury

• There is no time dependency of the data, while in clinical practice, de-escalation is generally performed when the patient is improving (and therefore the PK issues associated with critical illness may be partly normalized), and with a lower bacterial burden.

• Only 5 antibiotics were simulated, due to the unavailability of other population PK models

Conclusion

For a selection of microorganisms, the probability to achieve therapeutic exposure was lower for the narrower spectrum antibiotics using conventional dosing compared to the broad-spectrum antibiotics. However, changing the intermittent infusion to a higher dose continuous infusion improves this probability dramatically.

Acknowledgements

Mieke Carlier is funded by a predoctoral mandate from the Research Foundation Flanders. Jason Roberts is funded in part by a National Health and Medical Research Council of Australia Research Fellowship (NHMRC APP1048652). Jan De Waele is a senior clinical investigator from the Research Foundation Flanders.