



Renal Failure Related to Broad-spectrum Antibiotics in Critically Ill Patients Secondary End Point Results from a 1200 Patient Randomized Trial

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BACKGROUND

Critically ill patients are more vulnerable to organ-related drug toxicities than less severely ill patients. Trials assessing safety of broad-spectrum antibiotics in Intensive Care Unit (ICU) are generally scarce, underpowered for assessing organ failure endpoints, and do often not include defined kidney organ failure endpoints. In this secondary analysis from a randomized trial we aimed to determine whether ICU-patients receiving broad-spectrum antibiotics had a higher frequency of adverse renal outcomes, compared to patients receiving standard regime and if so, identify the antibiotics as the cause of such a renal failure.

METHODS

PASS is a randomized multi-center trial in 1200 critically ill adult patients. Patients were randomized either to standard strategy according to international clinical guidelines "standard exposure" group, or to same clinical guidelines but supplemented with daily drug-escalation initiated upon procalcitonin increase; "high exposure" group (Jensen et al, CCM 2011). 28-day mortality was comparable and was 31.8%. Organ failure and antibiotic exposure were followed-up for 28 days or until death. The use of piperacillin/tazobactam day 1-28 was significantly higher in the "high exposure" group compared to the "standard exposure" group (Figure 1). The endpoints explored were renal failure defined as eGFR <60 ml/min/1.73 m² ('ever' or 'number of days with') until day 28. Analysis was by intention to treat. NCT00271752.

RESULTS

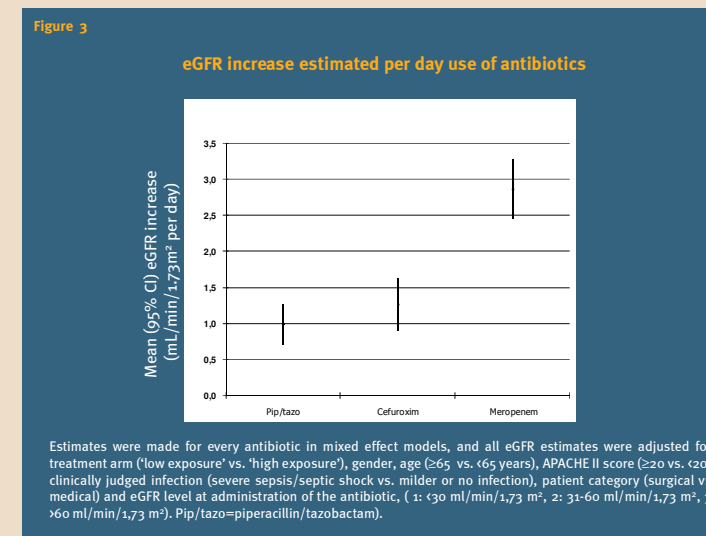
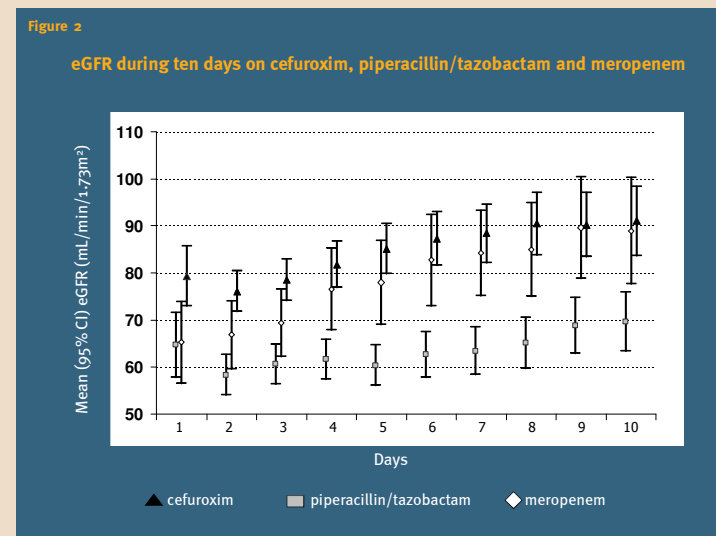
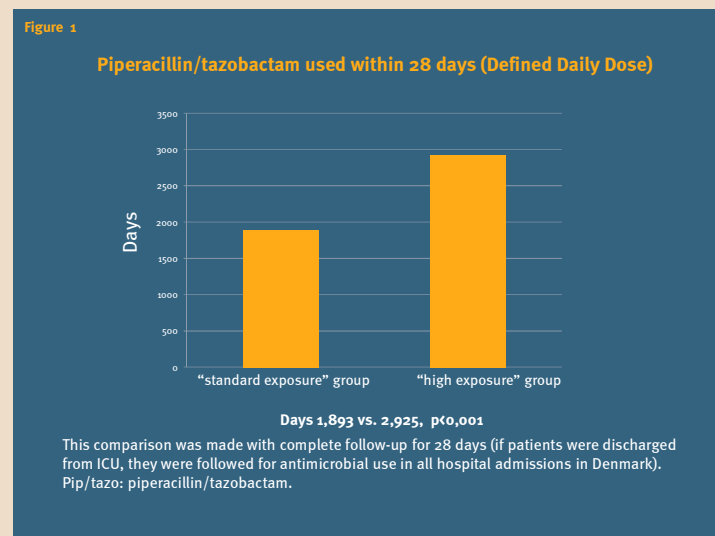
604 patients were allocated to the "high exposure" group and 596 to the "standard exposure" group; % with eGFR <60 ml/min in two groups at entry and at last day of follow-up was 57% vs. 55% and 41% vs. 39%, respectively.

The % of days spent with renal failure was 48% in the "high exposure" arm vs. 43% in the "standard exposure" arm, p<0.0001. Comparison of the eGFR of all patients for the first ten days showed the slowest recovery of renal function in patients on piperacillin/tazobactam as compared to patients on meropenem or cefuroxim (Figure 2).

A multiple effects model investigating the eGFR regression coefficient ("increase in eGFR") per day on these drugs confirmed that renal recovery was lowest in patients on piperacillin/tazobactam (Figure 3). After discontinuing piperacillin/tazobactam the renal recovery rate increased: 2.7 ml/min/1.73 m² /24h [95% CI: 2.3 - 3.1 ml/min/1.73 m²/24h].

CONCLUSIONS

Piperacillin/tazobactam was identified as a cause of delayed renal recovery in critically ill patients.



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