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PASS

Candida Infections Related to Broad-spectrum Antibiotics in Critically Ill Patients: secondary end point results from a 1200 patient randomised trial

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BACKGROUND

The possible role of broad-spectrum antibiotics in invasive candida infection (ICI) is not yet resolved. In this secondary analysis from a randomized trial, we aimed to determine whether a more intensive antibiotic strategy guided by change in a biomarker in critically ill patients does result in an increased incidence of ICI.

METHODS

PASS is a randomized trial in 1200 adult critically ill patients. Patients were randomized either to treatment according to current international guidelines (SOC) or to same guidelines but supplemented with daily drug-escalation, whenever procalcitonin was increasing ('high exposure'); 28-day mortality was comparable (Jensen et al, CCM 2011). The endpoints investigated were ICI and 'Possible Candida Infection'. Analysis was by intention to treat. NCT00271752.

RESULTS

604 participants were allocated to 'high exposure' (435 medical) and 596 to SOC (422 medical). The most often used broad-spectrum antibiotic was ciprofloxacin; the fraction of days, where this drug was used was 0.33 vs. 0.21, p<0.001. The HR (high exposure/SOC) for ICI was 1.9 [95% CI: 1.0 – 3.6] for medical (**Figure 1**) but not surgical patients. Use of ciprofloxacin, but not other drugs, independently predicted risk of 'possible candida infection' from day 4-28 (**Figure 2**) and a positive relation between the length of exposure and the risk of fungal infection was observed (**Figure 3**). Additionally, the use of ciprofloxacin on baseline was an independent predictor of 'invasive candida infection', likewise as the only antibiotic (HR: 1.9 [95% CI: 1.0 – 3.5]).

CONCLUSION

A strategy of higher exposure to broader-spectrum antibiotics leads to more invasive candida infections in medical patients. Use of ciprofloxacin, used as part of this strategy, was the only antibiotic agent independently associated with this excess risk.

Figure 1

Risk of 'Invasive Candida Infection' according to the randomly assigned groups

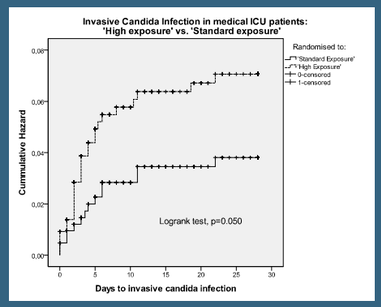


Figure 3

Risk of 'Possible Candida Infection' according to the length of exposure to ciprofloxacin

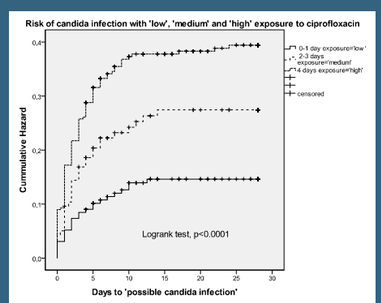
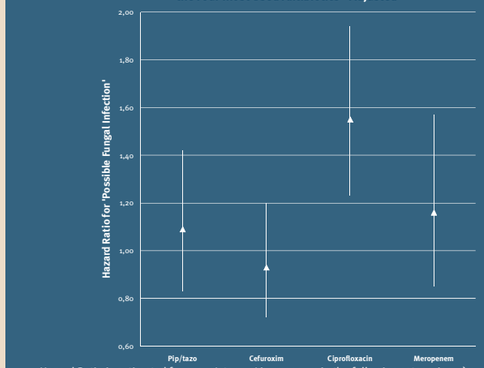


Figure 2

Adjusted risk of 'possible fungal infection'



Hazard Ratio is estimated for every 'step up' in exposure in the following categories: 1) 0-1 days use, 2) 2-3 days use, 3) 4 days use. Category 1 is reference. The model was adjusted for use of the antibiotics and antifungal prophylaxis. In a sensitivity analysis, we apart from use of antibiotics, also adjusted for all variables that were univariately associated with fungal infection (p<0.2), that is: Surgical patient (Y/N), Kidney Function at Baseline (1) <30 ml/min/1.73 m², 2) 30-60, 3) >61) , Mechanical Ventilation (Y/N). This did not alter the signal or statistics. Neither did stratifying the results for which arm the patient had originally been allocated to.

Participating sites

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