O381
2-hour Oral Session
New insights in the control of multi-resistant Gram-negatives

Impact of combination and sequential antibiotic therapies in selecting resistance

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Background: Although prior antimicrobial drug exposure is a risk factor for colonization due to an antibiotic-resistant bacteria (ARB), the temporal association between therapy and acquisition is still unclear due to a multifactorial process. The objective of the study was to define the impact of antibiotics in hospitalised patients according to combinations and sequential order of the treatments.

Methods: Two-year multicenter prospective European cohort study. Target microorganisms were methicillin-resistant *Staphylococcus aureus* (MRSA), ESBL-producers *Enterobacteriaceae*, and carbapenemase-resistant *Pseudomonas* and *Acinetobacter* (MDR-GN). Periodic screening were performed after starting antibiotic (3-7-14-30-day). The assessable population included all patients treated with antibiotics from whom a negative baseline and at least one follow-up screening in a 30-day period was available. A stepwise multivariate regression and a Support Vector Machine (SVM) analysis were used to find the most effective machine-learning model to deal with a multi-factorial and heterogeneous dataset.

Results: Overall 10,197 patients were included in the study providing 58,804 samples. At baseline 8,933 patients were not colonised. Among those, 4,160 started antibiotics for a total of 46,190 observed days of therapy (ODT). The cohort patients received 6,450 antibiotic treatments for a total of 52,775 ODT. Mean duration of therapy was 12.7 days (range, 1-27; SD 2.6) per patient. The most frequently prescribed antibiotics were cephalosporins (44%; 17,420 ODT) and quinolones (16.3%; 8030 ODT). The rate of new acquisition after starting antibiotics was 4.2% for MRSA and 23.5% for ESBL versus 1.7% and 10.9% in patients without antibiotic treatment, respectively. A stepwise regression approach showed that

patients, negative at hospital admission and taking antibiotic were 3-time more likely to develop colonization due to MRSA (RR: 3.9; 95%CI: 2.9-5.2) and 4-time more due to ESBL (RR: 4.4; 95%CI: 3.7-4.6). The association remains significant after adjusting for counfonders. The application of SVM identified the following combinations having the highest coefficients for acquiring ESBL strains (AUC 0.73): carbapenems and macrolides (12.56), linezolid and quinolones (11.00), penicillins and quinolones (8.80), and metronidazole and piperacillin (7.10). Among the monotherapy linezolid showed the highest risk of developing ESBL colonization (5.79) followed by amynoglycosides (5.06). The SVM identified also risks associated to the sequential use of antibiotics. Glicopeptydes following piperacillin (3.42) was associated to the highest risk. The highest coefficient for acquiring MRSA strains was observed for the combination of a cephalosporin and piperacillin (2.59) followed by the following sequential therapies: cephalosporins after daptomycin (2.26), metronidazole after cotrimoxazole (2), and penicillins after aminoglycosides (2) (AUC 0.59).

Conclusions: This study is the largest investigation ever conducted to assess the association between antibiotic treatment and selection of resistant strains analysing combination and sequential therapy. Combination therapies showed the highest risk in selecting ESBL and MRSA. Effect of monotherapy is strongly influenced from previous used antibiotics.