72
Antimicrobial Resistance among Gram-negative Isolates in Haematology-oncology Patients: Ecological Analysis in a University Hospital

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Background: Prophylactic treatment with oral fluoroquinolones, mainly levofloxacin in neutropenic patients has been found to be useful for preventing Gram-negative bacteraemia and has become a popular and standard preventive-therapy strategy in many cancer centres. Moreover, intravenous anti-pseudomonal antibiotics represent the first choice in empirical therapy of febrile neutropenic inpatients.
Objectives: To find a difference in the pattern of resistance of the evaluated organisms among hemato-oncologic patients after the introduction of quinolones prophylaxis, starting on 2002. Secondary aim was finding other statistically significative changes in pattern of resistance among the other considered classes of antibiotics.
Methods: Retrospective observational study was conducted considering significant isolates obtained from respiratory tract samples (tracheo-aspirates and BAL) and blood, urine and swabs cultures from inpatients of 2 hemato-oncology wards (30 beds) of San Martino University Hospital (Genoa, Italy) from 2000 to 2005. Two groups of pathogens were considered for the analysis: Gram-negative fermenters (GNF) (*Enterobacteriaceae*) and non fermenters (GNNF) (*P. aeruginosa*, *S. maltophilia*, *B. cepacia*, *A. baumannii*). The rates of resistance to 5 top used antibiotics: ciprofloxacin (CIP), amikacin (AMK), ceftazidime (CAZ), piperacillin-tazobactam (TZP) and imipenem (IMI) have been analysed. χ^2 test for statistical analysis was used.
Results: 185 GNNF and 597 GNF were isolated in the study period. Among GNF, we found a difference of resistance to CIP from (20% versus 34%, p=0.02) and to CAZ (3% versus 13%, p= 0.008), not for AMK, TZP and IMI. Among GNNF we have found no statistical differences of resistance crossing the years. For the detailed results see table.

GNF resistance	2000	2001	2002	2003	2004	2005
CIP	20%	21%	36%*	45%*	52%*	34%*
CAZ	3%	2%	7%	1%	7%	13%**

*Compared to year 2000 $p<0.02$, **compared to 2000 p=0.008.

Conclusions: A statistically significant trend in CIP and CAZ resistance among GNF has been found. Despite little number of isolates and the lack of clinical history and outcome of patients, our data showed that empirical treatment and popular levofloxacin prophylaxis have impact on the resistance ecology in the hemato-oncologic departments. The study underlines the importance of knowing the local "ward" epidemiology to optimise empiric antibiotic therapy.

73
Outcome with Early Oral Voriconazole Therapy in 73 AML-MDS Patients with Invasive *Aspergillosis*

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Background: Invasive aspergillosis (IA) is a leading cause of morbidity and mortality in patients with AML/MDS. Current standard of care is treatment with voriconazole. In the registration trial voriconazole was given intravenously for the first 8 days but the bioavailability of oral voriconazole is excellent. Therefore we decided to give voriconazole orally during the first 8 days of therapy if oral intake was possible. We here describe our experience in a large group of patients with AML/MDS and IA.
Methods: In 269 consecutive patients treated for AML/MDS from 2002 to 2007, evidence for IA was collected using HRCT for the evaluation of neutropenic fever and galactomannan measurement in broncho-alveolar lavage fluid of intrapulmonary lesions. IA was classified according to the recently updated EORTC-MSG definitions. All cause mortality 12 weeks after the start of antifungal therapy was registered. For the evaluation of attributable mortality of IA we compared all cause mortality 12 weeks after the last course of anti-leukemic therapy between patients with and without IA. Voriconazole treatment was given orally from day 1 whenever oral intake was possible. The same dosing regimen as was given intravenously in the study by Herbrecht et al was used orally (Herbrecht R et al. 2002).
Results: 80 patients developed IA, 48 (18%) of them had probable or proven infection and 32 (12%) had possible IA. 6 were treated with amphotericin-B in 2002 before voriconazole became available in the Netherlands and 1 patient received itraconazole. 73 patients were treated with voriconazole; 55 (75%) were able to take oral voriconazole from day 1. Overall mortality 12 weeks after the start of voriconazole was 22% (16/73). This compares favourably with the study by Herbrecht et al. where a 12 week overall mortality of 29% was reported with voriconazole and 42% when amphotericin-B deoxycholate was used. The overall mortality 12 weeks after the last course of anti-leukemic therapy was 26% in IA-patients compared to 16% in IA-free patients (p=0.06) with a hazard ratio of dying for patients with IA of 2.4 (95% CI, 1.3 -4.4) in a cox regression analysis.
Conclusions: Early diagnosis with HRCT, galactomannan measurement in BAL and treatment of IA with oral voriconazole results in an acceptable 12-week mortality.
Reference: Herbrecht R et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med. 2002 Aug 8;347(6):408-15.

74
Septifast PCR for the Microbiological Documentation of Infections in Febrile Neutropenic Patients

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Background: Blood cultures are the gold standard of microbiological diagnosis in febrile neutropenic patients. However, no causative agent is identified in 2/3 of febrile episodes. Septifast (Roche) is a new PCR test, which may detect bacterial and fungal DNA in blood (spectrum of 25 bloodstream pathogens).
Objective: To assess the utility of Septifast PCR for the microbiological documentation of febrile neutropenia.
Methods: Blood samples for blood cultures and Septifast PCR were prospectively drawn in 100 adult neutropenic cancer patients at D0 (onset of fever) and D3 (if persistent fever). Febrile episodes were classified as microbiologically (MDI) or clinically documented infection (CDI) and fever of unknown origin (FUO) according to the results of blood cultures.
Results: 237 samples were analyzed in 146 febrile episodes (51 MDI, 51 CDI, 44 FUO). Blood cultures and Septifast were positive in 39 (27%) and 51 (35%) episodes, respectively. The pathogens were: