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FLUOROCHINOLONE-RESISTANT ESCHERICHIA COLI IS THE MOST FREQUENT PATHOGEN ISOLATED FROM PATIENTS WITH HEMATOLOGIC MALIGNANCIES. RESULTS OF A PROSPECTIVE STUDY ON 364 CONSECUTIVE EPISODES OF FEVER AT A SINGLE INSTITUTION

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Background. Regular monitoring of the bacterial epidemiology at hematologic units has been recommended in order to evaluate the effects of the prophylactic and empiric antibacterial strategies adopted. Aims. To disclose the most frequent pathogens involved in infectious complications and the emerging resistance to antibiotics. Methods. We analysed all the consecutive febrile/infectious episodes occurring to the 823 patients admitted to our Institution (248 Acute Leukemia, 233 Lymphoma, 195 Myeloma, 26 Myelodysplastic Syndrome, 28 Chronic Lymphocytic Leukemia, 10 Myeloprolypherative Syndrome and 83 non neoplastic haematological patients) from June '04 to September '05. All the patients with expected neutropenia lasting for more than 7 days received prophylaxis with levofloxacin 500 mg/day. Results. Three hundred and sixty-four cases developed fever/infection (44.2% of all admission) and in 188 cases (51.6%) an infection was clinically documented (bacteremia 46%, pneumonia 42%, urinary tract infections 7%, others 5%). One hundred and sixty-four pathogens were isolated in 137 microbiologically documented infections (37.6%) including 82 Gram- bacteria (50%), 66 Gram+ bacteria (40.2%), 14 fungi (8.5%) and 2 miscellaneous (1.3%). E. coli, Enterobacteriaceae other than E. coli, and Pseudomonas spp were the most relevant Gram- strains (respectively 23.2%, 9.8% and 10.4% of all isolates). Among Gram+, S. aureus, Coagulase-negative Staphilococci (CoNS) and Enterococci were the most frequent pathogens, accounting respectively 15.2%, 11% and 7.9% of all isolates. E. coli was statistically more frequent in patients affected by acute leukaemia (26/69, 38% vs 10/68, 15%, p<0.01), neutropenia <500/mm3 (31/81, 38% vs 7/56, 13%, p<0.01) and on prophylaxis with levofloxacin (28/66, 42% vs 8/43, 19% p<0.05) S. aureus was associated with a non controlled underlying disease (24/91, 26% vs 1/46, 2%, p<0.01), neutrophil count >500/mm3 (20/56, 36% vs 5/81, 6%, p<0.01) and absence of prophylaxis with levofloxacin (11/43, 26% vs 3/66, 5%, p<0.01). Presence of central venous catheter (CVC) did not significantly predispose to CoNs infections (16/98, 16% vs 2/39, 6%, p=NS). Gram- bacteria showed resistance to Fluoroquinolones (FqR) in 42/61 cases (68.9%) associated by multivariate analysis only to prophylaxis with levofloxacin (OR 9.88, IC 2.32-42.01, p=0.002). Specifically FqR-resistant E. coli represented 91.7% of E. coli isolates (33/36). Hence it represented the pathogen most frequently isolated (21.3% of all isolates) among hematooncologic patients admitted to our Institution. Sixteen of the 25 (64%) Staphilococcus spp showed resistance to methicillin (MR), which was associated by multivariate analysis to prophylaxis with levofloxacin (OR 15.68, IC 1.03-238.13, p=0.047) and to CVC (OR 20.23, 1.34-305.69, p=0.03), but not to hospitalisation. Conclusions. In contrast with the recently reported prevalence of Gram+ bacteria in most haematological units, a shift toward Gram- bacteria, particularly FqR E.coli, was observed in our Institution. The role of levofloxacin prophylaxis in changing the epidemiological pattern and inducing FqR and MR needs further investigation.

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SIGNIFICANCE OF ENDOTHELIAL MICROPARTICLES, PLATELETS, AND LEUKOCYTE ACTIVATION IN PATIENTS WITH ACUTE CORONARY SYNDROME

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Backgrounds. The details of interactions between endothelium, platelets, and leukocytes in ACS are not well understood. Aims. The purpose of this research was to determine the levels of platelet, leukocyte, and endothelial activation and markers of cellular interactions in patients with acute coronary syndrome (ACS). Methods. We studied 55 patients with VTE and compared 55 healthy controls. We used flow cytometry to measure: 1) endothelial microparticles (EMP) identified by $CD31^+/CD42b^-$ (EMP(31)) or E-selectin (EMP(62E)); 2) platelet microparticles ($CD31^+/CD42b^+$); 3) surface expression of P-selectin in platelets and CD11b in leukocytes; 4) EMP-monocyte conjugates (percentage of monocytes positive for E-selectin); and 5) platelet-leukocyte conjugates (PLC) expressed as percentage of leukocytes positive for CD41. *Results.* Patients with ACS had marked elevations of EMP(31) (2,213 vs. 372 counts/microl; p<0.01), EMP(62E) (379 vs. 231 counts/microl; p = 0.001), and EMP-monocyte conjugates (3.2% vs. 2.3%; p<0.01), as well as increased activation of platelets (31.9 vs. 4.8 fluorescence intensity units for P-selectin; p<0.001) and leukocytes (12.5 vs. 6.9 U for CD11b; p = 0.01). Also elevated in ACS were PLC (59.6% vs. 37.4%; p<0.01). Expression of CD11b in leukocytes strongly correlated with PLC (r = 0.64; p<0.001). Conclusions. Marked activation of endothelium, platelets, and leukocytes occurs in ACS, which involves the release of EMP and formation of EMP-monocyte conjugates and PLC. These findings support prior studies suggesting that release of EMP and their binding to monocytes are key events in thrombogenesis. Our findings also support the concept that the formation of PLC regulates leukocyte activation and participates in linking thrombosis with inflammation.

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CIRCULATING ENDOTHELIAL PROGENITOR CELLS IN PATIENTS WITH ANCA-ASSOCIATED VASCULITIS

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Introduction. There are two essential types of endothelial cells circulating in blood. First type are mature endothelial cells (CECs), which numbers are increased in microcirculation disorders such as ANCA associated small vessels vasculitis (AAV). These cells are connected with vascular damage. The other type are circulating endothelial progenitor cells (EPCs), which originate from bone marrow and play a crucial role in vascular repair and cancer neoangiogenesis. AIM. As there are several works studying mature CEC in patients with AAV, we have explored the frequency of immature EPCs in these patients. Methods. Circulating EPC numbers were determined in 35 patients with AAV, including 16 patients with newly diagnosed active disease without prior immunosuppressive treatment, 15 patients with active disease already treated by immunosuppressive therapy (pulse i.v. cyclophosphamide and peroral corticosteroids) and 10 patients in remission of the disease. Six patients were investigated twice (at diagnosis and in remission). We have used three groups of controls: 15 patients with non-AAV renal damage (patients on long-term hemodialysis), 9 patients suffering from macrocirculation disorders (ischemic disease of lower extremities) and 23 healthy volunteers. EPCs were enumerated by colony forming unit assay. 15-20ml of peripheral blood was centrifuged on Ficoll-Hypaque gradient (Pharmacia, Uppsalla, Sweden) and mononuclear fraction was cultivated in the EndoCultTM medium (StemCell Technologies, Vancouver, Canada) according to manufacturer instructions. Clusters of at least 20 central round cells surrounded by spindle-shaped cells were counted as endothelial precursor colonies. Results. The number of EPC was significantly lower in patients with AAV compared to healthy volunteers (median 0,5 vs. 12,3 EPC-CFU/ml blood, p<0,001). We did not find any statistical difference in numbers of EPC among groups of AAV patients before and after beginning of treatment and a group of patients in remission on maintenance immunosuppression. We have also found no correlation between the number of EPC and the Birmingham Vasculitis Activity Score (BVAS), level of C-reactive protein, plasma creatinine or titre of ANCA. Patients with ANCA anti-PR3 antibodies had a trend toward lower numbers of EPC compared to those with anti-MPO antibodies (median 0,18 vs. 3,15 EPC-CFU/ml blood, p=0,08). The number of EPC in patients on long-term hemodialysis was also significantly lower than in healthy volunteers (median 1,9 vs. 12,3 EPC-CFU/ml blood, p=0,001) and not statistically different from the number of EPCs found in patients with AAV. Patients with macrovascular disorders had non-significantly lower numbers of EPCs compared to healthy volunteers and significantly higher than patients with AAV (6,18 v. 0,5, p=0,035). CONCLUSION: Contrary to higher numbers of mature circulating endothelial cells, numbers of circulating endothelial precursors are significantly lowered in patients with ANCA positive vasculitis. This may reflect serious endothelial damage on one hand, coupled with diminished ability of endothelial healing. Immunosuppressive treatment, which is frequently also cytotoxic, may suppress not only the microvascular inflammation but also the endothelial healing process. Low numbers of EPCs in patients with terminal kidney disease may reflect the accelerated atherosclerosis found in uremia.

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