

OVERT GASTROINTESTINAL BLEEDING IN PATIENTS WITH HEMATOLOGIC DISEASE

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Abstract

Background. Patients with hematologic disease are at risk for gastrointestinal bleeding due to multiple factors: haemostasis impairment, gastrointestinal toxicity of chemotherapy, high dose corticotherapy, severe gastrointestinal and systemic infections.

Aim. A retrospective study on the incidence, etiology, clinical evolution and therapeutic particularities in patients with primary hematological disease.

Patients and Methods. A retrospective, observational, single center study, during 2005-2009, in the Hematology Department of the 1st Medical Clinic from Tg.Mureș Emergency County Hospital. Out of 5259 admissions for primary hematologic disease, 36 patients developed gastrointestinal bleeding during their admission to the hospital. We analysed the following data: hematologic diagnosis, associated comorbidities, haemostasis impairment, use of chemotherapy and/or corticotherapy, etiology, treatment and outcome. Data was analysed using GraphPadPrism 2004 for Windows, chi square test.

Results. Gastrointestinal bleeding incidence was 0.6845% out of a total of 5259 hospital admissions, the rebleeding rate 5.55%, inpatient mortality 33.33%, the main cause of death being not gastrointestinal bleeding per se, but septic shock. Upper versus lower gastrointestinal bleeding ratio was 4.5. Endoscopic haemostasis was performed in 2 patients. No surgery was performed. Gastrointestinal bleeding correlates statistically significant with inpatient mortality ($p < 0.0001$). Though the severity of gastrointestinal bleeding does not differ statistically significant (benign versus malignant hematologic disease, $p = 0.2134$), mortality was zero in patients with benign hematologic disease, all having clinically significant impaired haemostasis.

Conclusions. Gastrointestinal bleeding is not a frequent complication of hematologic disease, but correlates with higher mortality, without being the direct cause of death. Indirectly it reflects a general altered status, mostly in patients with malignant hematologic disease.

Keywords: gastrointestinal bleeding, chemotherapy, high dose corticotherapy.

HEMORAGIA DIGESTIVĂ LA PACIENTUL HEMATOLOGIC

Rezumat

Introducere. Factorii care predispun pacientul hematologic la hemoragie digestivă sunt multipli: diateza hemoragică, toxicitatea gastrointestinală a chimioterapiei, corticoterapia în doze mari, infecțiile severe digestive și sistemice.

Scop. Studiul incidenței, etiologiei, evoluției și particularităților terapeutice în hemoragia digestivă la pacientul hematologic.

Material și metodă. Studiu retrospectiv observațional desfășurat în Clinica Medicală I - Compartimentul de Hematologie al Spitalului Clinic Județean de Urgență Tg. Mureș în perioada 2005-septembrie 2009. Din totalul de 5259 internări pentru afecțiuni primare hematologice, 36 de cazuri, din care 35 cu diateză hemoragică,

au prezentat hemoragie digestivă. Am analizat: boala hematologică primară, comorbidități, statusul coagulării, chimioterapie sau corticoterapie utilizată, etiologia, tratamentul și evoluția. Datele au fost analizate folosind programul Graph PadPrism 2004 pentru Windows, testul chi pătrat.

Rezultate. Incidența hemoragiei digestive raportată la numărul internărilor a fost de 0.6845%, cu o recurență de 5.55%, mortalitate intraspitalicească de 33.33%. Raportul hemoragie digestivă superioară versus inferioară a fost de 4.5, 3 cazuri prezentând simultan hemoragie digestivă superioară și inferioară. S-a efectuat hemostază endoscopică în 2 cazuri. Nu s-a intervenit chirurgical în nici un caz. Hemoragia digestivă se corelează semnificativ statistic cu mortalitatea intraspitalicească ($P < 0.0001$). Deși severitatea hemoragiei nu diferă semnificativ statistic (benign versus malign, $p = 0.2134$), mortalitatea a fost 0 la pacienții cu hemopatii benigne, toți prezentând anomalii ale hemostazei.

Concluzii. Hemoragia digestivă nu complică frecvent hemopatiile, fiind corelată cu o mortalitate intraspitalicească ridicată, fără a constitui însă cauza decesului. Indirect, reflectă statusul general alterat al pacientului cu hemopatie malignă.

Cuvinte cheie: hemoragie digestivă, chimioterapie, corticoterapie în doze mari.

Background

The hematologic patient, especially the one with malignant disease, can develop multiple complications due to primary hematologic disease, radio- and chemotherapy, associated comorbidities [1,2]. There are multiple risk factors for gastrointestinal bleeding in such patients: primary or secondary haemostasis impairment (haemophilia, idiopathic thrombocytopenic purpura, postchemotherapy thrombocytopenia) [3], gastrointestinal toxicity of chemotherapy, which very often includes high dose corticotherapy, also used for immunosuppressive or cytoreductive purposes [2,4,5]. Comorbidities associated to age, as well as hematologic primary disease, are an important factor [2,5]. Very often, the hematologic patient is in a very altered general status that does not allow to perform gastrointestinal endoscopy for diagnosis purpose, or surgical treatment. Examples include: toxico-septic shock associated to febrile neutropenia, severe pancytopenia, multiple system organ failure, severe acute respiratory failure, mediastinal compression syndrome, tumoral lysis syndrome and its complications, to remind just a few situations from clinical practice [1,4,5].

Aim

We could not reach any information regarding the features of gastrointestinal bleeding in haematologic patients and decided to search this complication in this particular group of patients.

We studied gastrointestinal bleeding in terms of incidence, etiology, clinical evolution and therapeutic aspects in hematologic patients, both with benign and malignant pathology. Identifying particular aspects of

gastrointestinal bleeding in this group of patients would allow extra prophylactic measures in terms of monitoring and therapy.

Methods

Observational, single center, retrospective study, during 2005-2009, at the 1st Medical Clinic-Hematology Department from Târgu Mureș Emergency County Hospital. Out of 5259 admissions for primary hematologic disease, 2097 presented clinically significant haemostasis impairment. Thirty five out of 36 patients with gastrointestinal bleeding presented clinically significant haemostasis impairment, mainly due to severe thrombocytopenia. Patients with variceal upper gastrointestinal bleeding or with haemostasis impairment due to hypersplenism associated to cirrhosis were not included in our study.

Gastrointestinal bleeding was diagnosed based on clinical data, mainly bleeding exteriorisation: hematemesis, melena, hematochesia or rectoragy. Hemoglobin level decrease was not a valuable diagnosis tool or severity criteria in some patients, mainly due to postchemotherapy status or ongoing chemotherapy, with haemoglobin values decreasing due to other causes than gastrointestinal bleeding. Also, blood pressure or pulse were not used as severity criteria for gastrointestinal bleeding due to a high percentage of patients with sepsis, especially in patients with hematologic malignancy. Upper or lower digestive tract diagnostic endoscopy was performed in 21 patients. Endoscopy could not be performed in all cases due to a poor general status, often before exitus, in patients under palliative care.

Surgery was not performed in none of the cases. All patients on chemotherapy for hematologic malignancy, as well as patients with autoimmune thrombocytopenia

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treated with high-dose corticotherapy, received prophylactic proton pump inhibitors, before the onset of gastrointestinal bleeding. Treatment included: proton pump inhibitors, endoscopic haemostasis, specific (coagulation factors products) and non-specific haemostatic drugs (vitamin K, adrenostasin). Data were statistically analysed using GraphPadprism2004 for Windows, chi square test.

Results

Out of 5259 of admissions for primary hematologic disease, 0.68%, representing 36 patients, developed gastrointestinal bleeding. 35 patients (97.22%) with gastrointestinal bleeding presented clinically significant haemostasis impairment. Malignant versus benign hematologic disease ratio was 2:1, diagnosis distribution being detailed in table number I. Medium age was 58.36 years, with a minimum of 19 years and a maximum of 82 years old, the sex ratio being 1.26 (20 males, 16 women).

Table II. Gastrointestinal bleeding exteriorisation.

| Exteriorisation | Cases (% total) |
|-----------------|-----------------|
| Hematemesis | 17 (47.22%) |
| Melena | 26 (72.22%) |
| Hematochesia | 1 (2.77%) |
| Rectoragy | 6 (16.66%) |

Gastrointestinal lesions, endoscopically diagnosed when possible, were as follows: 6 cases of gastric ulcer, 1 case of duodenal ulcer, 6 cases of diffuse haemorrhagic gastritis, 1 gastric polip, 1 case of postgastrectomy haemorrhagic gastritis, 4 cases of hemorrhoidal disease, 1 case of rectal tumour. We mention 2 patients with chronic myeloproliferative syndrome, both thrombocytopenic, who developed portal vein thrombosis and cavernoma, who had grade I oesophageal varices, but in whom upper gastrointestinal bleeding was caused by gastric ulcers. Both cases had a favourable outcome. Another patient with type A haemophilia, severe form, presented a massive lower

gastrointestinal bleeding, as well as hemoperitoneum, following surgery (jejunectomy and termino-terminal anastomosis) for intestinal occlusion. The haemorrhagic source was suspected to be at the anastomosis level, the evolution being favourable after substitutive treatment with VIIa recombinant factor (Novoseven) and VII, IX and X coagulation factors (Feiba). One single case, with a normal coagulation status, presented upper gastrointestinal bleeding exteriorised by small quantity red vomitus, the cause being a severe oesophagitis following radiotherapy for mediastinal lymphoma with compression syndrome. The patient died because of respiratory failure due to bronchopneumonia on lungs, with fibrosis secondary to radiotherapy for mediastinal lymphoma. One patient presented severe haemorrhagic stomatitis.

We found no statistically significant correlation between the incidence of severe forms of gastrointestinal bleeding and the type of hematologic disease (malignant versus benign, $p=0.2134$, odds ratio=1.950, 95% confidence interval: 0.3687-10.31). Overall inpatient mortality was of 33.3%, rebleeding being encountered in 2 cases. Mortality correlated statistically significant with malignancy, this being zero in patients with benign hematologic disease (6 cases of haemophilia-5 congenital, 1 acquired, 4 cases of thrombocytopenia-2 autoimmune, 2 postmedication). There were no deaths in patients with chronic myeloproliferative syndromes, 3 of them having essential thrombocytosis and 3 idiopathic myelofibrosis, so no case of chronic granulocitary leukemia. Mortality for each hematologic diagnosis is detailed in table number 1. Though a statistically significant risk factor for inpatient mortality ($p<0.0001$, odds ratio=13.48, 95% confidence interval: 6.857-26.52), gastrointestinal bleeding was the cause of death in few cases (8.33%), the incidence of haemorrhagic shock being of 11.11%, the main cause of death being septic shock in patients often with febrile neutropenia (66.66%). Mortality in patients with upper

Table I. Gastrointestinal bleeding in patients with hematologic disease: incidence and correlation with inpatient mortality according to primary hematologic diagnosis (O.R.: odds ratio, C.I.: confidence interval).

| Hematologic disease | Gastrointestinal bleeding cases (% out of total admissions with the mentioned diagnosis). | Mortality (%) | Gastrointestinal bleeding as a risk factor for in-patient mortality (p value-chi square test), O.R., 95%C.I. |
|---|---|---------------|--|
| Haemophilia | 6 (6.74%) | 0 (0%) | - |
| Trombocytopenia (3-autoimmune-idiopathic, 3 postmedication) | 6 (0.19%, 0.21% out of severe forms) | 0 (0%) | - |
| Chronic myeloproliferative syndrome | 6 (22.22%) | 0 (0%) | - |
| Acute leukemia | 7 (3.04%) | 5 (71.42%) | $P<0.0001$, O.R.= 31.86 95% C.I.: 7.470 to 135.9 |
| Lymphoma | 4 (0.26%) | 3 (75%) | $P<0.0001$, O.R.:41.64 95%C.I.: 8.883 to 195.2 |
| Chronic lymphocytic leukemia | 2 (0.74%) | 2 (100%) | $P<0.0001$, O.R.= 26.70 95%C.I.: 3.404 to 209.4 |
| Multiple myeloma | 3 (0.31%) | 1 (33.3%) | $P<0.0001$, O.R.=39.71 95%C.I.: 3.718 to 424.1 |
| Myelodysplastic syndrome-refractory anemia with blasts excess | 2 (0.91%) | 1 (50%) | $P<0.0001$, O.R.=261.0 95%C.I.: 8.405 to 8105 |
| Total | 36 (0.68%) | 12 (33.3%) | $P<0.0001$, O.R.=13.48 C.I.: 6.857 to 26.52 |

gastrointestinal bleeding did not correlate significantly statistic with the use of corticotherapy, usually included in high doses in most chemotherapy regimens ($p=0.4517$, 95% confidence interval: 0.2287-3.683). Also, it did not correlate with chemotherapy regimen application during current admission in hospital ($p=0.0897$, 95% confidence interval: 0.06458 to 1.264).

Discussions

Currently, gastroenterology treatment guidelines [6,7,8,9,10,11,12,13] do not have specific recommendations for hematologic patients or with clinically significant haemostasis impairment, probably due to the fact that hematologic disease per se is rarely the cause of gastrointestinal bleeding [2,12,14,15]. Hematology guidelines make recommendations for haemorrhagic complications in general, emphasizing on medical treatment and prophylactic measures of haemostasis impairment, but less on endoscopic therapy or the role of surgical treatment [14].

From the prognostic point of view, hematologic patients can be divided in two main categories: 1. the patient with benign hematologic disease, in our study being included patients with haemostasis impairment due to haemophilia and autoimmune thrombocytopenia; 2. the patient with hematologic malignancy under chemotherapy, with secondary thrombocytopenia, with or without underlying gastrointestinal disease.

Our study includes 6 patients with gastrointestinal bleeding in patients with type A haemophilia, all of them with severe forms, representing 4.44% of the total admissions of haemophilic patients, respectively 20% of patients with hemophilia during the mentioned period.

The literature [16,17,18,19,20,21,22,23] does not provide too much data on gastrointestinal bleeding in haemophilic patients, mainly because of two perfectly understandable factors: haemophilia is a rare disorder, now treatable with substitution of the deficient coagulation factor. The literature provides us mainly case reports or studies on limited number of patients, the etiology of gastro-intestinal bleeding being not very different than that of the non-haemophilic patient [22,24,25], but with some more interesting and rare causes, such as intestinal angioleiomyoma, spontaneous mural haematoma, ruptured arterial pseudoaneurism, jejunal hemangioma. Treatment is mainly based on correcting the coagulation status with substitutive treatment of the deficient factor and less on endoscopic or surgical methods, surgery being usually avoided in haemophilic patients. A 10 years (1975-1985) retrospective survey in the U.S.A. [22] reports an incidence of 10.3% for gastrointestinal bleeding in 243 haemophilic patients (25 patients, 43 gastrointestinal bleeding episodes). Duodenal ulcer was the main cause of gastrointestinal bleeding, in 22% of cases. Gastritis was responsible for 14% of cases. In 22% of cases the etiology of gastrointestinal

bleeding could not be mentioned. Endoscopic studies show the fact that the etiology of gastrointestinal bleeding did not differ statistically significant between haemophilic and non-haemophilic patients. Hematology guidelines [14] do not make specific recommendations on gastrointestinal bleeding, but only general recommendations regarding major bleeding episodes. Major bleeding episodes, with important vital risk, include any gastrointestinal bleeding, big joints and muscular bleeding, posttraumatic bleeding, central nervous system bleeding, cervical, iliopsoas bleeding as well as forearm bleeding. Immediate treatment is recommended, preferably in the first 2 hours from the onset. Light and moderate forms of type A haemophilia can be treated with **desmopressin**; severe forms, without inhibitors can be treated with factor VIII concentrate. Gastrointestinal endoscopy is a useful and safe diagnostic tool, after the correction of factor VIII level of minimum 0.4U/ml. As in non-haemophilic patients, *Helicobacter Pylori* infection and the use of non steroidal anti-inflammatory drugs are important risk factors for upper gastrointestinal bleeding, according to several studies [18,23,24].

Another particular clinical situation is represented by the patient with autoimmune thrombocytopenia, with acute massive upper gastrointestinal bleeding. Currently available gastroenterology guidelines do not make specific recommendations for this kind of particular situations, perfectly understandable because such cases are extremely rare. For instance, a reported case of severe upper gastrointestinal bleeding in a female patient with rheumatoid arthritis and secondary autoimmune thrombocytopenia was resolved endoscopically (bleeding gastric polyp), high dose corticotherapy being reintroduced 2 days after endoscopic haemostasis, with the correction of thrombocytopenia and a favourable outcome [26,27]. It is very interesting the fact that several studies, among which a recent systematic review [28], shows the fact that *Helicobacter Pylori* eradication also improves thrombocytopenia in 50% of patients, without knowing or understanding the exact mechanism. On the other hand, a multicenter controlled trial showed no benefit of *Helicobacter Pylori* eradication on correcting thrombocytopenia in patients with idiopathic thrombocytopenic purpura. Out of 55 patients, one from the control group (without treatment for *Helicobacter Pylori* eradication) developed upper gastrointestinal bleeding due to severe thrombocytopenia which required high dose Prednisone [26,27].

From the coagulation status point of view, the initial purpose is to obtain more than 30.000 platelets/mm³, or the so called "haemostatic platelet count" and then to increase the number also taking into consideration possible side effects of the treatment. For patients on Aspirin, nonsteroidal antiinflammatory drugs, chronic anticoagulation and other antithrombotic therapies, maintaining a level of over 40.000-50.000 platelets/mm³ is recommended. Correction

of platelet levels is indicated in all patients with a level under 20.000 cells/mm³ or who develop bleeding episodes [27,29].

Chemotherapy regimens used for haematologic malignancies have a gastrointestinal toxicity in 100% of patients, under different forms and of different severity, but gastrointestinal bleeding per se has a relatively low incidence [1,30,31]. An endoscopic study [31] performed on patients with acute leukemia under chemotherapy regimens found oesophagitis in 50.9%, gastric erosions in 30.2% and gastritis in 22.6% of patients. The same study concludes that endoscopy is a relatively safe diagnostic tool, but the percent of endoscopic haemostasis in this category of patients was relatively low. A recent study [30], actually the only one we found in the literature to have studied the incidence of gastrointestinal bleeding in patients with hematologic malignancies found a global incidence of 7.1% of patients who developed gastrointestinal bleeding, representing 5.7% of patients with acute leukemia, 1.9% of patients with chronic leukemia. In our study, the incidence of gastrointestinal bleeding is very low in terms of hospital admissions but very similar in terms of the total number of patients who required repeated admissions during a few years time: 6.9% of patients with hematologic malignancy (including lymphoma, multiple myeloma, acute and chronic forms of leukemia), 8.5% of patients with acute leukemia, 5.1% of patients with chronic leukemia developed gastrointestinal bleeding. Gastrointestinal bleeding correlated with the blastic phase of the disease, according to the same study [30]. As in our study, gastrointestinal endoscopy could be performed only in 8 out of a total of 25 cases, due to the altered general status of the patients. Overall mortality was 21.875%, compared to our study where it was 33.33%. As in our study, gastrointestinal bleeding was not the direct cause of death, but an important contributing factor. Also, data regarding upper versus lower gastrointestinal bleeding incidence ratio are similar (3.56 versus 4.5, in our study).

Another major risk factor for gastrointestinal bleeding is represented by severe gastrointestinal or systemic infections [32,33], an important element which is also found indirectly in our results, the overall mortality being mainly caused by toxico-septic shock, but we did not register any case of lower gastrointestinal bleeding associated to neutropenic enterocolitis. At this moment, there are no large studies [14,34] on the treatment of neutropenic enterocolitis, a severe pathology, the treatment being individualised for each patient. Initially, conservative treatment is recommended, persistent gastrointestinal bleeding despite the correction of cytopenia or coagulation disorder being an indication for surgery [34,35].

Conclusions

Gastrointestinal bleeding in patients with haematologic malignancy is not a commonly encountered

complication, but is often a particular clinical situation from a diagnosis and therapeutic point of view. Despite the fact that the etiology of gastrointestinal bleeding does not differ from the non-haematologic patient, the management of such patients requires a multidisciplinary approach, which involves: gastroenterology, hematology, intensive care, surgery. Our data is concordant with recent literature regarding gastrointestinal bleeding in patients with hematologic malignancies, but less recent available data regarding gastrointestinal bleeding in haemophilic patients. Overall mortality is significantly influenced by gastrointestinal bleeding, but in an indirect manner, the main cause of death in these patients being toxico-septic shock with multiple system organ failure. In patients with hematologic malignancy undergoing chemotherapy, gastrointestinal bleeding usually reflects a severely altered general status and indirectly a high risk for exitus. The patient with benign hematologic disease, mainly with a coagulation disorder, who develops gastrointestinal bleeding has a good prognosis in the conditions of early treatment, mainly based on correcting the haemostasis impairment combined with antisecretory medication, and less on more invasive procedures, either endoscopic or surgical ones.

References

1. Kawamura S., Sawada Y., Fujiwara S., Kawatsu S., Chiba Y., Yoshida Y. Clinical and pathologic studies of gastrointestinal hemorrhage in acute leukemia. *Tohoku J Exp Med* 1979;127 (4):345-352.
2. Karaoglu A.O., Kadikoylu G., Yukselen V., Yasa M.H., Bolaman Z. Gastrointestinal lesions and *Helicobacter Pylori* in patients with myeloproliferative disorders. *Saudi Med J* 2004; 25(12):1913-1916.
3. Maher A.A., Collins J.M., Olden K.W., Kelly K.A. Spontaneous Intramural Small Bowel Hematoma-Clinical Presentation and Long-term Outcome. *Arch Surg* 2002; vol.13, www.archsurg.com.
4. Pamuk G.E., Öüztürk E., Demir M. Successful treatment of severe gastrointestinal bleeding after chemotherapy in acute myeloblastic leukemia with recombinant activated factor VII-report on one case and review of other uses in acute leukemias. *Med Oncol* 2009; epub ahead of print, www.pubmed.com.
5. Gorschlütter M., Schmitz V., Mey U. et al. Endoscopy in patients with acute leukaemia after intensive chemotherapy. *Leuk Res* 2008;32 (10):1510-1517.
6. Celinski K., Cichoz-Lach H., Madro A. et al. Non-variceal upper gastrointestinal bleeding-guidelines on management. *J Physiol Pharmacol* 2008;59(Suppl2):215-229.
7. Vorburger S.A., Candinas D., Egger B. Acute lower gastrointestinal bleeding-an evidence based algorithm for diagnosis and treatment. *Ther Umsch* 2006 May, 63(5):301-309.
8. Gschossmann J.M., Netzer P. Acute upper gastrointestinal bleeding. *Ther Umsch* 2006 May;63(5):291-294.
9. Harty R.F., Ancha H.B. Stress ulcer bleeding. *Curr Treat Options Gastroenterol* 2006;9(2):157-166.
10. Constantin V.D., Păun S., Ciofoaia V., Budu V., Socea B.

Multimodal Management of Upper Gastrointestinal Bleeding Caused by Stress Gastropathy: *J Gastro Liv Dis* 2009;18(3):279-284.

11. Grigorescu M., Beuran M.: Actualități în diagnosticul și tratamentul hemoragiilor digestive superioare. Cluj Napoca: Editura Teognost, 2006.

12. Rockett D.C. Gastrointestinal Bleeding. In: Sleisenger and Fordtran's Gastrointestinal and Liver Diseases. 8th Edn, Philadelphia: Saunders, 2006, 255-301.

13. Pascu O. Hemoragiile digestive. In: Gastroenterologie Hepatologie-Bazele practicii clinice, 2nd Edn, Cluj Napoca: Editura Medicală Universitară "Iuliu Hațieganu" Cluj-Napoca, 2006, 71-96.

14. Mahlangu J.N., Gilham A. Medical and Scientific Advisory Council of the South African Haemophilia Foundation. Guideline for the treatment of haemophilia in South Africa: *S Afr Med J*. 2008;98:126-140;

15. Braden B., Wenke A., Karich H.J. et al. Risk of gastrointestinal bleeding associated with *Helicobacter Pylori* infection in patients with hemophilia or von Willebrand's syndrome. *Helicobacter* 1998; 3(3):184-187.

16. Sun C., Sui T., Liu W., Yang R. Gastrointestinal bleeding attributable to a small intestine angioleiomyoma in a patient with haemophilia A. *Haemophilia* 2009; 15(1):355-356.

17. Martinez Cecilia D., Torres Tordera E.M., Arjona Sánchez A. et al. Spontaneous intramural small bowel hemorrhage: an event on the increase. *Gastroenterol Hepatol* 2007;30(6):331-333.

18. Eyster M.E., Asaad S.M., Gold B.D. et al. (Second Multicenter Hemophilia Study Group). Upper gastrointestinal bleeding in haemophiliacs: incidence and relation to use of non-steroidal antiinflammatory drugs. *Haemophilia* 2008; 13(2):221-224.

19. Nour K., Nour Y., Ben Yahmed A., Bedioui H., Ben Abid H., Menif E. Spontaneous false aneurysm of the gastroduodenal artery in a hemophilic patient ruptured into the duodenum: a case report. *Abdom Imaging* 2006;31(1):43-44.

20. Ramadan K.M., Lowry J.P., Wilkinson A., McNulty O., McMullin M.F., Jones F.G. Acute intestinal obstruction due to intramural haemorrhage in small intestine in a patient with severe haemophilia A and inhibitor. *Eur J Haematol* 2005; 75(2):164-166.

21. Fozza C., Bellizzi S., Piseddu G., Porcu A., Dore F., Longinotti M. Spontaneous intramural intestinal haemorrhage in a haemophilic patient. *Br J Haematol* 2004; 125(4):419.

22. Mittal R., Spero J.A., Lewis J.H. et al. Patterns of gastrointestinal hemorrhage in hemophilia: *Gastroenterology* 1985;88(2):515-522.

23. Szczepanik A.B., Zaleska M., Wiszniewski A. et al. *Helicobacter Pylori* infection in patients with haemophilia in Poland: prevalence and risk of upper gastrointestinal bleeding. *Haemophilia* 2005;11(4):376-379.

24. Schulman S., Rehnberg A.S., Hein M. et al. *Helicobacter Pylori* causes gastrointestinal bleeding in patients with congenital bleeding disorders. *Thromb Haemost* 2003; 89(4):741-746.

25. Treepongkaruna S., Sirachainan N., Kanjanapongkul S. et al. Absence of platelet recovery following *Helicobacter Pylori* eradication in childhood chronic idiopathic thrombocytopenic purpura: a multicenter randomized controlled trial. *Pediatr Blood Cancer* 2009;53(1):72-77.

26. Gál I., Tóth L., Szegedi L., Kiss G.G. Gastric Bleeding in a patient with rheumatoid arthritis complicated by immune thrombocytopenic purpura: *Joint Bone Spine* 2008; 75(3):350-352.

27. Douglas B., Bussel J.B. How I treat idiopathic thrombocytopenic purpura: *Blood* 2005;1(7):2244-2251.

28. Arnold D.M., Bernotas A., Nazi I. et al. Platelet count response to *H. pylori* treatment in patients with immune thrombocytopenic purpura with and without *H. Pylori* infection: a systematic review. *Haematologica* 2009;94:850-856.

29. Salama A., Rieke M., Kiesewetter H., von Depka M. Experiences with recombinant FVIIa in the emergency treatment of patients with autoimmune thrombocytopenia: a review of the literature. *Ann Hematol* 2009; 88(1):11-15.

30. Soyulu A.R., Buyukasik Y., Cetiner D. et al. Overt gastrointestinal bleeding in haematologic neoplasms. *Dig Liver Dis* 2005;37(12):917-922.

31. Gorschlütter M., Schmitz V., Mey U., Hahn-Ast C., Schmidt-Wolf I.G., Sauerbruch T. Endoscopy in patients with acute leukemia after intensive chemotherapy. *Leuk Res* 2008; 32(10):1510-1517.

32. Lucia J.F., Aguilar C., Betran A. Blastocystis hominis colitis in a haemophilic patient as a cause of lower gastrointestinal bleeding. *Haemophilia* 2007; 13(2):224-225.

33. Davila M.L. Neutropenic enterocolitis: *Curr Treat Options Gastroenterol* 2006; 9(3):249-255.

34. Colovic N., Rajic Z., Sretenovic M., Stojkovic M., Colovic M. Neutropenic enterocolitis in acute myeloid leukemia. *Acta Chir Iugosl* 2004; 51(2):127-131.

35. Zhenglun Zhu. Gastrointestinal Manifestations of Immunodeficiency. In: *Current Diagnosis and Treatment- Gastroenterology, Hepatology and Endoscopy* by Greenberger N.J., Blumberg R.S., Burakoff R., 1st Edn, McGrawHill Lange, 2009, 131-134.