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MANAGEMENT OF BACTERIAL COLONISATIONS IDENTIFIED IN PAEDIATRIC PATIENTS WITH ONCO-HAEMATOLOGIC DISORDERS WHO UNDERWENT HEMATOPOIETIC STEM CELL TRANSPLANTATION

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The current complex paraclinical approach to paediatric onco-haematological diseases has led to increased survival of these patients. The acute or chronic, infectious or immune complications occurring in the paediatric patient undergoing the hematopoietic stem cell transplant procedure generated systematized measures of bacterial screening and qualitative/quantitative analysis of the gut microbiome with the aim of decreasing the morbidity and mortality of these patients. Analysis of the microbiota by NGS (next generation sequencing) is a topical approach with a favourable impact in the adaptation and individualization of treatment for the oncological patient, but with increased implications of human and financial resources. The identification of bacterial colonisations with adapted therapy applied reduces the risk of infection and qualitatively characterizes the gut microbiota, dysbiosis. Modulation of the microbiome is the basis of the prevention and treatment of diseases of the entire digestive tract.

Keywords: colonisation, haematopoietic stem cell transplantation (HSCT), dysbiosis, screening, gut microbiota, infection, sepsis, mucositis.

INTRODUCTION

The current approach, generated by the continuous refinement of diagnostic, treatment and monitoring protocols, of paediatric onco-haematologic disorders has led to increased survival rate, even to 85% at 5 years, and to individualized therapies with decreased toxicity and without affecting the remission rate [1-3]. In spite of these continuously adapted management strategies, an important percentage of patients with haemato-oncological disorders, present a disease with high risk of relapse or a relapse/ refractory disease, which requires haematopoietic stem cell transplantation (HSCT) as a therapeutic conduct. Infection related mortality, the important cause of non-relapse mortality in this particular category of immunosuppressed paediatric patients with cancer who undergo HSCT, has led to the particularisation of bacterial screening [4-6]. Strict monitoring with the identification of digestive bacterial colonisations, an important source of bacterial translocation in the immunosuppressed paediatric patient, requires a therapeutic conduct adapted to decontamination with the aim of decreasing the risk of acute or chronic local and/or systemic complications with a direct impact on increasing the survival rate of these patients [7]. Dysbiosis, the qualitative/quantitative changes in the saprophytic flora in the digestive tract generated by: the stress of onco-haematological disease, the application of complex treatment that requires multiple regimens of cytotoxic chemotherapy and prophylactic antibiotic therapy, is the basis of immune and infectious complications of at the level of the digestive tract [8]. Among the frequent complications, generated by the alteration of the microbiome of the entire digestive tract, from the oral cavity to the anus, I mention: mucositis with damage to the integrity of the entire dentoalveolar apparatus, gastritis, typhlitis, colitis, rectocolitis, etc. or intestinal graft versus host disease (GVHD). All of them can have an acute, systemic, serious evolution with an increase in the morbidity and mortality of these patients [9]. That is why we consider that the analysis of the gut microbiota, a recently approached paraclinical method, is becoming desirable in terms of cancer prophylaxis, screening, treatment and even monitoring. It is known that: the alteration of the function and composition of the gut microbiota produces chronic inflammation, decrease of local immunity with the onset of infections and growth and proliferation of cells, with the modification of the metabolism of food and drugs or other biochemical functions of the host with an impact on the evolution of the disease, the treatment, of nutritional status with the worsening of the patient's condition and with the increase of morbidity and mortality [8]. Therapeutic intervention for the modulation of gut dysbiosis leads to the prevention of long- and short-term complications, with a decrease in the higher consumption of financial and material resources necessary to treat onco-haematologic disorders and with an increase in survival rate [10,11]. The present paper proposes the analysis of digestive colonisations, identified by rectal swab and the evaluation of their impact, in paediatric patients with onco-haematologic disorders who underwent hematopoietic stem cell transplantation (HSCT).

MATERIALS AND METHODS

An analytical, observational, cohort, prospective study that included a group of 15 paediatric patients with a haemato-oncological diagnosis who underwent haematopoietic stem cell transplantation (HSCT) procedure was conducted between January and July 2023, in the Paediatric clinic, HSCT department, of Fundeni Clinical Institute, Bucharest.

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The Paediatric Clinic of Fundeni Clinical Institute is a university clinic within "Carol Davila" University of Medicine and Pharmacy, so all hospitalized patients are informed and express their written consent by signing the informed consent form to participate in studies and in everything that involves the forms of university education, complying with the rights of the patient and the current norms of national and European medical ethics.

Colonisations were identified by performing a rectal swab, a standardized internal procedure for the immunosuppressed paediatric patient, in the Paediatrics clinic of Fundeni Clinical Institute.

Screening was conducted to detect bacterial colonisations by collecting 4 samples: the first - at admission; the second in a week, after decontamination, on HSCT day; the third sample when the patient was in severe aplasia or had other complications, e.g.: mucositis, sepsis, etc. The last sample was collected before discharge.

The prophylactic antibiotic treatment applied to the subjects included in the study is standardized, according to the internal procedure of the Paediatric Clinic of Fundeni Clinical Institute, for the HSCT procedure and usually consisting of the administration of: fluoroquinolones, sulfamethoxazole/trimethoprim (for Pneumocystis prophylaxis), antifungal (fluconazole) and antiviral (acyclovir) treatment.

The statistical analysis was performed with the Excel program and IBM SPSS Statistics 20 - for the statistical associations the Chi-Square test (Fisher's exact test) was used.

PURPOSE

Identification of bacterial colonisations in children with onco-haematologic disorders with the aim of the therapeutic conduct adapted to prevent complications in order to increase the survival rate of these patients.

OBJECTIVES

1. Demographic analysis of the batch
2. Analysis of patients according to the type of onco-haematologic diagnosis
3. Analysis of patients according to the type of HSCT procedure
4. Analysis of the hematopoietic stem cells pre-transplant therapeutic profile
5. Identification of multidrug-resistant bacteria (MDRB) colonisation
6. Assessment of the impact of colonisations on acute and chronic complications

WORKING HYPOTHESES

Main hypothesis: Identification of strains by rectal swab in patients with negative stool culture test represents a step in the identification of individual taxonomic groups, conditionally pathogenic, but with an impact in preventing acute systemic/local complications in paediatric patients undergoing HSCT.

Secondary hypothesis: The strains identified by rectal swab are strains that are selected from one's own gut microbiota that under certain conditions (food, stress, antibiotic therapy, chemotherapy, etc.) change their profile and become conditionally pathogenic, independent of contamination with new strains.

RESULTS

1. Demographic analysis of the batch

Figure 1. Distribution of patients according to environment of origin

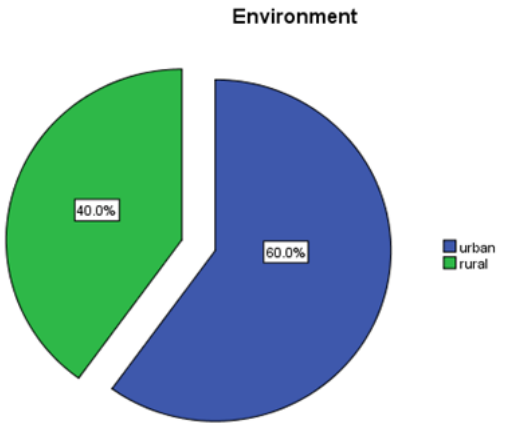
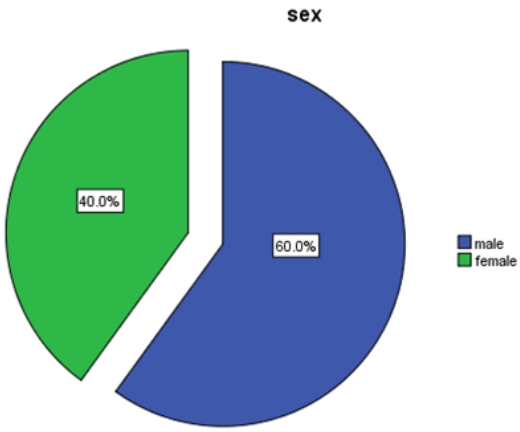
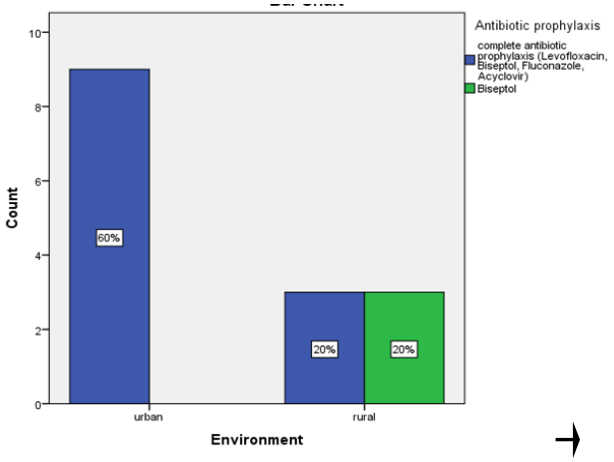


Figure 2. Distribution of patients according to sex



The environment of origin was statistically significantly associated with the antibiotic prophylaxis applied, p = .044, df = 1 (the urban environment more frequently received complete antibiotic prophylaxis).

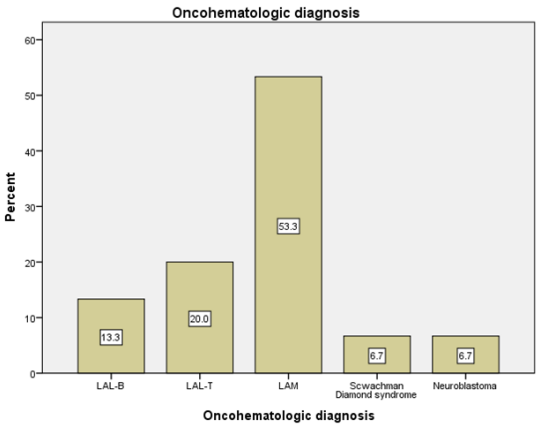
Figure 3. Distribution of patients according to the antibiotic prophylaxis applied and environment of origin



2. Analysis of patients according to the type of onco-haematological diagnosis

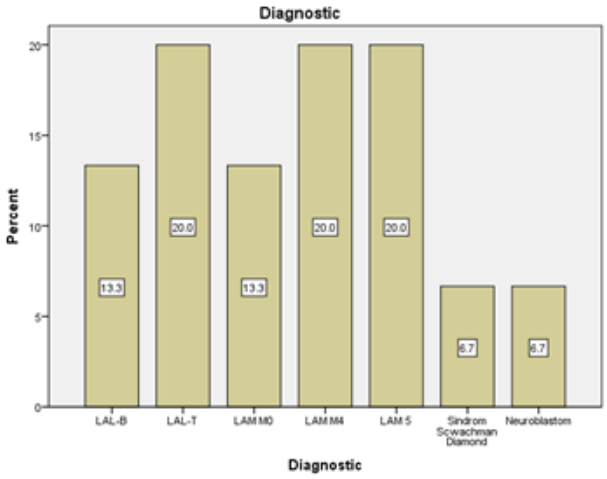
Figure 4. Distribution of patients according to diagnosis

3.



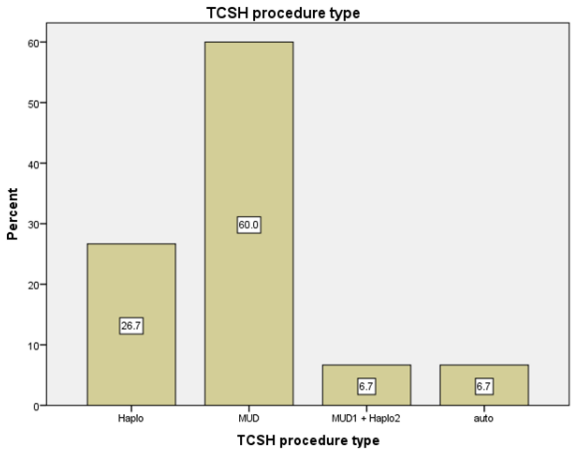
Analysis of patients according to the type of HSCT procedure

Figure 5. Distribution of patients according to the morphological type of leukaemia



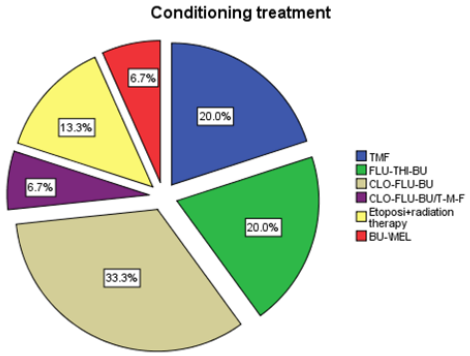
4. Analysis of the hematopoietic stem cells pre-transplant therapeutic profile

Figure 6. Distribution of patients according to the type of HSCT



Conditioning regimen applied
Antibiotic and antifungal prophylaxis administered to the subjects

Figure 7. Distribution of patients according to the conditioning treatment before HSCT



The intensity of the conditioning treatment was statistically significantly associated with the antibiotic prophylaxis applied, p = .010, df = 5.

Figure 8. Distribution of patients according to antibiotic prophylaxis

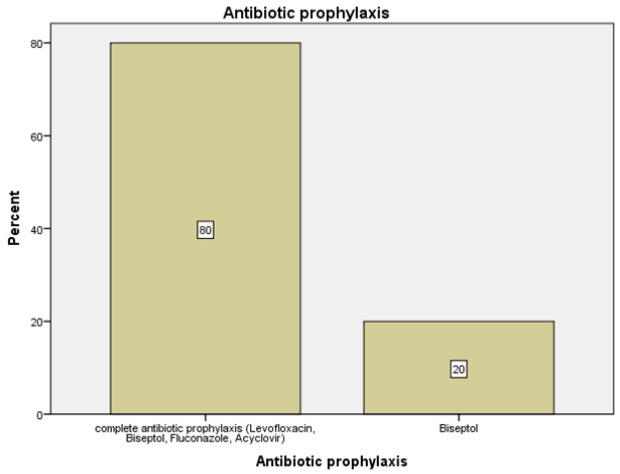
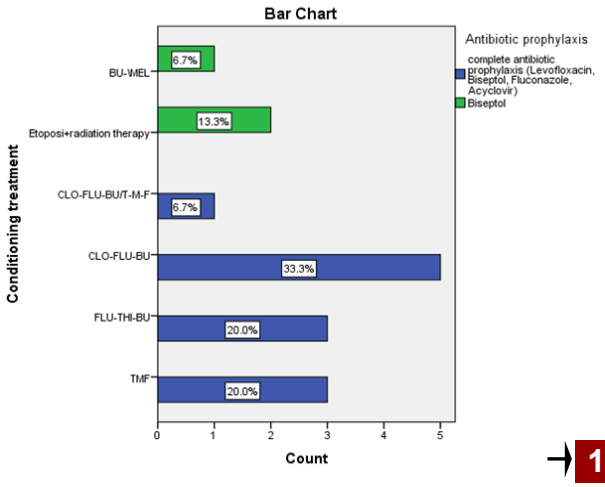


Figure 9. Distribution of patients according to conditioning treatment and antibiotic prophylaxis applied



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5. Identification of multidrug-resistant bacteria (MDRB) colonisation

Table 1. Colonisation result

Samples	Positive		Negative	
	No.	%	Nr.	%
Sample 1	4	26.7	11	73.3
Sample 2	4	26.7	11	73.3
Sample 3	4	26.7	11	73.3
Sample 4	2	13.3	13	86.7

a) Before applying the conditioning treatment (Sample 1)

Figure 10. Distribution of patients according to bacterial colonisation – Sample 1

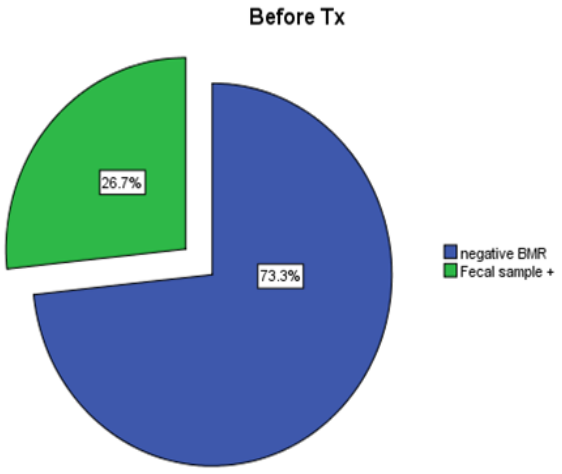
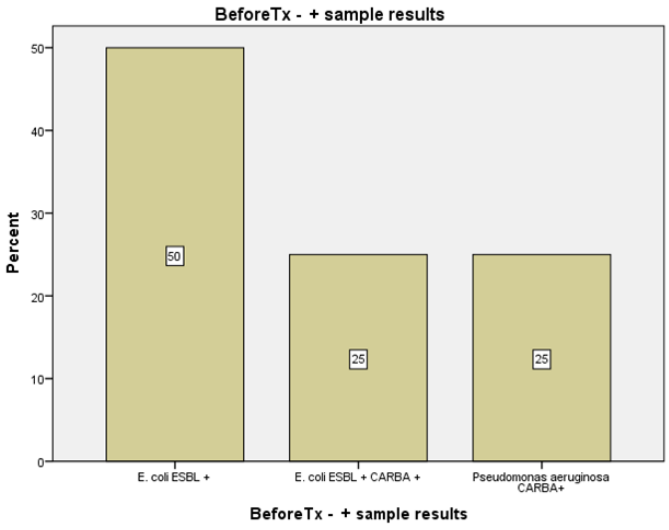
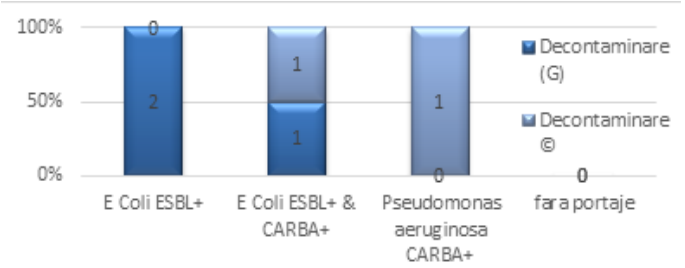


Figure 11. Identification of bacterial colonisations – Sample 1



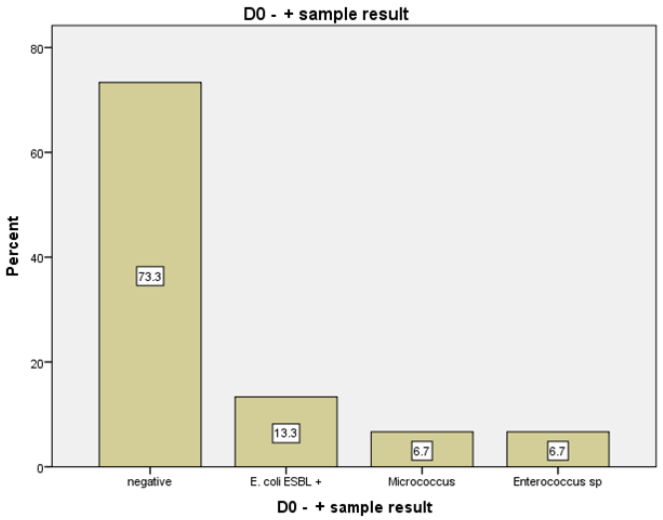
b) Digestive decontamination according to the colonisation

Figure 12. Distribution of patients according to the bacterial portage and applied decontamination



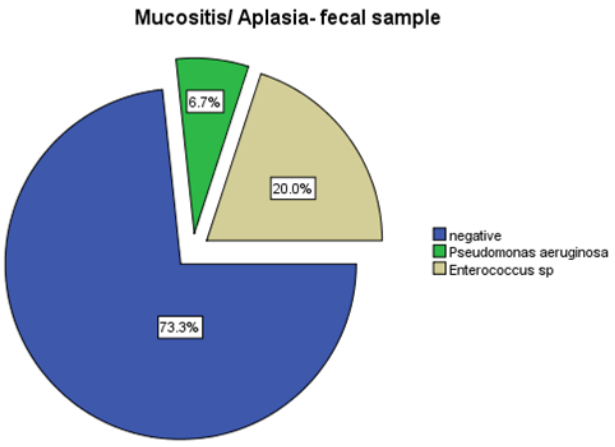
c) Assessment after decontamination (Sample 2)

Figure 13. Distribution of patients according to bacterial colonisation - Sample 2



d) Colonisations when complications are present (mucositis) (Sample 3)

Figure 14. Distribution of patients according to bacterial colonisation – Sample 3



Assessment of the impact of colonisations on acute and chronic complications (Sample 4)

Figure 15. Distribution of patients according to positive blood cultures

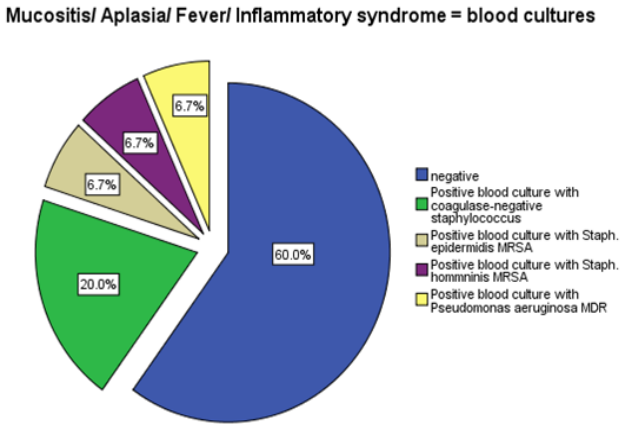
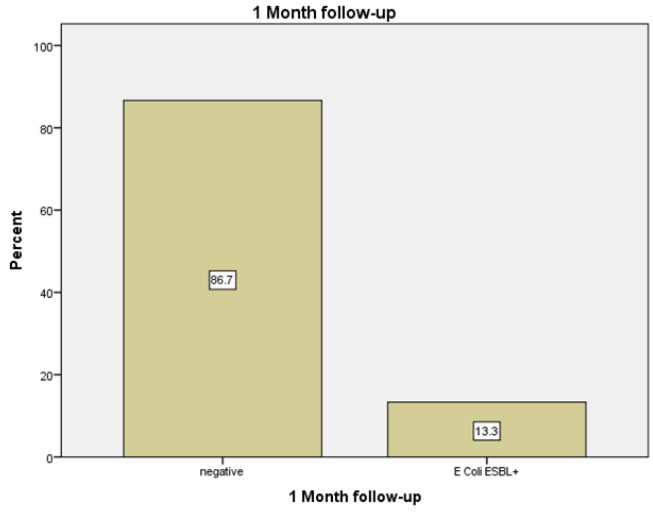


Figure 16. Distribution of patients according to bacterial colonisation – Sample 4



DISCUSSIONS

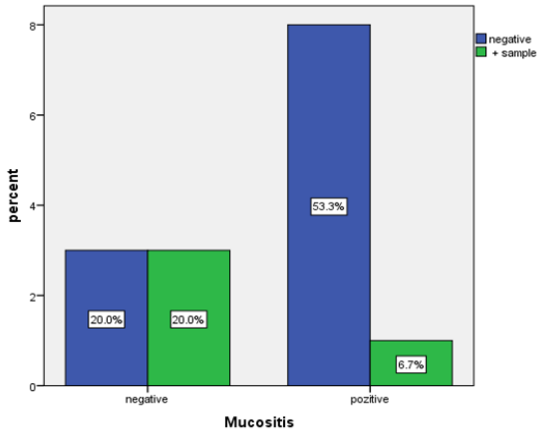
The main goal of this study was the post-doctoral project with the theme "Gut microbiome analysis in the immunosuppressed patient with onco-haematological diagnosis who underwent the hematopoietic stem cell transplantation procedure". Analysis of the microbiota by NGS (next generation sequencing) is a topical approach with a favourable impact in the adaptation and individualization of treatment for the oncological patient, but with increased implications of human and financial resources. The sequencing equipment and the test kit being expensive and at this time a test not reimbursed by the state led to the delay in the collection of the first samples for assessment of the microbiome through NGS, so the first sample was tested in June 2023. The samples from three patients from the analysed group have been collected and are currently in the test phase and they will represent the scientific basis of the following papers.

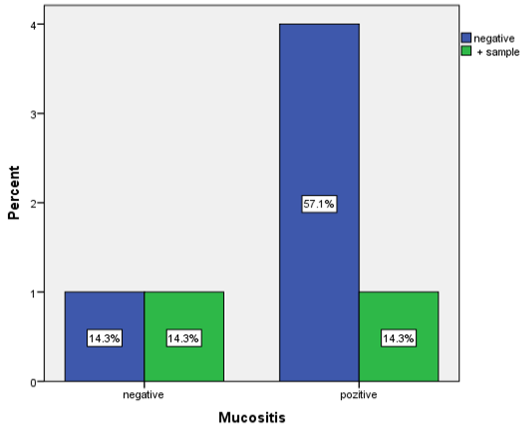
The present paper describes an analytical, observational, cohort, prospective study with the aim of identifying bacterial colonisations, dysbiosis of the oncological patient, with a major impact on local and systemic complications.

The batch included 15 patients who underwent the HSCT procedure during the selected period, the first six months of 2023, who met the selected criteria. The apparently low number of patients included in the present study is impactful because the Pediatric clinic of the Fundeni Clinical Institute has the highest addressability in the field in the country, having the highest number of pediatric HSCT procedures in Romania, approximately 30 per year.

The demographic analysis of the batch showed the predominance of male patients 9/15, coming from the urban environment 9/15, which is similar to the literature data [12,13]. The increased incidence of paediatric cancer in the male sex and the influence of the environment of origin on the intestinal microbiota are known. Among these factors we mention: type of diet (positive factors: increased consumption of fresh fruits and vegetables, protein of animal origin from a safe and good quality source, low consumption of fast food, etc.), source of drinking water (approved or certified) etc. [14-17]. The environment of origin, the level of education of the parents that

Figures 17-18. Evolution of subjects with colonisations identified in sample 1 and 2 and the occurrence of acute complications





influence the children's nutrition, along with the intake of pre and probiotics and food supplements (omega, vitamin D, zinc etc.) represent only a few of the factors influencing the intestinal microbiome [17]. Qualitative/quantitative changes in the saprophytic flora in the digestive tract are the basis of dysbiosis, colonisation, source of acute/chronic complications. In the present study, the environment of origin was statistically significantly associated with the antibiotic prophylaxis applied, p = .044, the urban environment received complete antibiotic prophylaxis more frequently compared to those from the rural environment.

In this study, the diagnosis of acute myeloblastic leukaemia (AML) prevailed in 8/15 cases: 2/8 AML-M0; 3/8 AML-M5; 3/8 AML-M4, followed by acute lymphoblastic leukaemia (ALL) 5/15 cases: 3/5 T-cell ALL and 2/5 B-cell ALL and 2/15 cases other diagnoses (1/2 neuroblastoma and 1/2 Shwachman-Diamond syndrome). The distribution by type of diagnosis complies with the HSCT indication recommended by international guidelines. Although ALL is a more common condition compared to AML in paediatric patients, the indication for HSCT is less frequent (forms with unfavourable response to standard treatment, refractory, or with high-risk genetic changes etc.) compared to paediatric patients with AML in whom the indication for HSCT is recommended, in most cases, in the first remission, which justifies the higher number of HSCT procedures in children diagnosed with AML in our study [18].

The conditioning treatment applied before HSCT varies depending on the diagnosis and the type of procedure [19]. In the studied group, 10/15 patients underwent alloHSCT: 9/10 MUD (matched unrelated donor) and 1/10 MSD (match sibling donor), 3/15 patients underwent haploHSCT and 1/10 autoHSCT. Related conditioning regimens included chemotherapy regimens as follows: 6/15 Clo-Flu-Bu, 4/15 Flu-Tio-Bu, 3/15 T-M-F, 2/15 Etoposide_Iradiation. The data are consistent with current EBMT recommendations [19]. Chemotherapy regimens (myeloablative or low-intensity regimens) along with the complex therapy administered to the oncological patient (antibiotic prophylaxis, immunosuppression, cortisone, proton pump inhibitors etc.) have a severe impact on the gut microbiota, with the selection of antibiotic-resistant bacterial taxonomic groups [20-22]. Also, paediatric oncology patients, being multi-hospitalized, are subject to an increased risk of contamination with resistant bacteria that, in conditions of immunosuppression, become a source of digestive infection, generating severe complications, regardless of the changes in the already existing flora.

All subjects included in the selected group are paediatric patients with onco-haematologic disorders that required multiple hospitalizations, complex, long-term chemotherapy, prophylactic and curative antibiotic, antifungal and antiviral therapy, prior to hospitalization in the HSCT department, which already implies a modification of the pathogenic flora at the level of the entire digestive tract independent of the complex treatment associated with the HSCT transplant procedure [19].

The prophylactic antibiotic treatment applied to the subjects included in the study is in compliance with the recommendations of the international protocols and with the specialized literature [20-23].

Among the colonisations identified by bacterial screening (rectal swab), we mention the following: *E. coli* ESBL+ 6/15; *E. coli* ESBL+ and CARBA+ 2/15; Enterococcus 2/15, Micrococcus 1/15 and Pseudomonas 2/15. Subjects had negative stool culture tests throughout the study. These ESBL+ (extended spectrum beta-lactamase) and/or CARBA+ bacteria are Gram-negative bacteria, which are normally found in the gut microbiota, enterobacteria capable of producing enzymes that hydrolyse and inactivate penicillin, cephalosporin and/or carbapenem antibiotics. Beta-lactamase-producing Enterobacteriaceae are the most frequent microorganisms identified in the dysbiosis of oncological patients, their incidence being continuously increasing [24]. The therapeutic decontamination approach is required in situations of immunosuppression to prevent bacterial translocation, secondary bacteraemia with multidrug-resistant bacteria (MDRB), to decrease the risk of acute local / systemic infection (sepsis) [20-23].

The first sample to identify colonisations, the one at admission, was performed before the start of the conditioning treatment. Most patients, 11/15 subjects, had negative colonisation screening cultures. In 2/15 *E. coli* ESBL+ was identified, in 1/15 *E. coli* ESBL+ and CARBA+ and 1/15 showed colonisation with *Pseudomonas aeruginosa* CARBA+. Digestive decontamination was applied for 7 days, according to the internal procedure with oral Gentamicin and Colistin, and the colonisations tested negative: 1/15 *E. coli* ESBL+; 1/15 *E. coli* ESBL+ and CARBA+; including the one with Pseudomonas was negative. An exception is the *E. coli* ESBL+ subject that remained positive despite administration of digestive decontamination treatment, which supports individualized internal microbial resistance mechanisms [25]. They are multiple and complex and form the basis of the formation of the ideal habitat for aberrant bacterial growth under the pressure of antibiotics, immunosuppression, proton pump inhibitors with the generation of an altered microbiome [26]. It is important to mention the identification of Piocyanic colonisation in a severely immunosuppressed patient, which represents a source of increased risk of infection [27].

The colonisations identified during the first screening are part of the ESKAPE group of organisms (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter species*), multidrog resistant bacteria (MDRB), responsible for severe infections in critically ill patients [28]. In this case, the application of decontamination treatment and systematized bacterial screening are required, especially for this category of patients [29-30].

At the next assessment of colonisations, after the end of the conditioning treatment, on the day of HSCT, sample 2, it was noted: the negativisation of previously discussed colonisations (3/15), the appearance of new colonisations in 2/15 subjects. They were initially negative, and at this determination we identified colonisations with: Enterococcus 3/15 and *E. coli* ESBL+ 1/15.

It is important to discuss about the subject with positive colonisation, in the first sample, with *Pseudomonas aeruginosa* 1/15, after the application of decontamination with Colistin, it tested negative, but presented colonisation with Micrococcus. This micro-organism present in

the normal gut microbiota is also a Gram-positive coccus that can generate local and systemic infections with serious evolution, especially in immunocompromised patients, which demonstrates a particular dysbiosis of this patient and requires treatment with systematized monitoring and bacterial screening [31].

When the patients had severe oral mucositis, severe post-chemotherapy aplasia, febrile syndrome, inflammatory syndrome, the colonisations identification tests were repeated and the only colonisation that came back positive was the one with *Pseudomonas aeruginosa* CARBA+.

Stool samples were also collected from the patients in the batch at the time of the appearance of the modified stool. This was negative in all subjects included in this study.

Other dysbiosis identified are: *Enterococcus faecium* in 3/15 patients, two 2/3 initially negative, 1/3 with *E. coli* ESBL+ dysbiosis from the beginning. These frequent colonisations within the group of selected patients, severely immunosuppressed children, require decontamination and systematic screening.

All patients in whom screening colonisation were identified and decontamination was performed, despite the complications present (severe immunosuppression, post-chemotherapy aplasia, grade III-IV mucositis, sepsis) had negative cultures for the bacteria identified in colonisations, except for the one with *Pseudomonas aeruginosa* CARBA+. The positive blood cultures were mostly with *Staphylococcus epidermidis* MRSA, infections independent of the digestive source. The identification of strains by rectal swab in patients with negative stool culture tests has a positive role in preventing acute systemic/local complications in paediatric patients undergoing HSCT, hypothesis supported and verified. Patients had negative stool culture test.

The patient with *Pseudomonas aeruginosa* CARBA+, a bacterium resistant to carbapenems, identified in the bacterial colonisation, negative stool culture test, under initial decontamination treatment tested negative, but at the time of severe aplasia it evolved and produced systemic infection, pyocyanic sepsis. This high-risk situation in a severely immunosuppressed patient (post chemotherapy – myeloablative conditioning treatment applied to perform the HSCT procedure), multi-hospitalized and treated with multiple antibiotics requires complex and intensive treatment (antibiotic therapy regime with multiple antibiotics according to the antibiogram) and strict monitoring. The evolution of the patient was favourable, which supports the screening, monitoring and therapeutic intervention of decontamination/treatment of patients in this category with the aim of decreasing morbidity and mortality.

At the last assessment of bacterial colonisations, performed at discharge, approximately one month after admission to the HSCT department, the reappearance of dysbiosis with *E. coli* ESBL+ was observed in a single subject with positive bacterial colonisation with *E. coli* ESBL, negative after decontamination, which remained negative throughout complications, but with recurrence before discharge. So, the identification of strains by rectal swab in patients with negative stool culture tests represents a step in the identification of individual taxonomic groups. The subject screening positive for *E. coli* ESBL+ quasi-constantly despite decontamination supports this assumption. The secondary hypothesis can be verified, but it requires the analysis of the gut microbiome through NGS to identify individualized taxonomic groups/patients prior to the application of the therapies and the assessment of their evolution under the applied complex treatment. *E. coli* ESBL+ strains are the strains of the gut microbiota which, under the influence of certain factors, become conditionally pathogenic, MDR bacteria, and modify the intestinal biofilm causing other secondary dysbiosis [24-25], the analysis of the gut microbiome through NGS is required.

Although most subjects presented local complications (oral mucositis, gastritis, even intestinal GVHD, only one patient presented systemic infection with digestive starting point and all survived.

It should be mentioned that the self HSCT procedure requires less intensive treatment compared to alloHSCT, treatment applied to only one subject in the group, he did not present positive colonisation complications, except for oral mucositis.

All included patients received during hospitalization a balanced, oncological diet, customized for age stages, complete in terms of dietary principles: carbohydrates with the lowest possible sugar content, lipids mainly from vegetable sources and high-quality proteins (dairy, white meat) with fresh and pasteurized foods. An attempt was made to apply a diet as uniform as possible. Cereals were from a varied spectrum: wholemeal flour, oats, rye, buckwheat, quinoa. The fruits are consumed in the form of compotes or in sponge cakes or pelts with minimal sugar content. Cooked vegetables were steamed, boiled, baked. Consumption of white meat and beef, well prepared thermally. Dairy: UHT cheese, UHT milk, pasteurized honey and chicken and quail eggs. Consumption of yogurt was limited, because it contains live micro-organisms and in immunocompromised children it can contaminate the flora with the production of a digestive infection. They also receive limited intake of raw fruits and vegetables, except: banana and avocado. It should be noted that there were deviations from this regimen due to: mucositis, changes in taste and even smell in the context of the application of the chemotherapy regimen, the presence of nausea and vomiting in the context of emetic chemotherapy or due to the capricious appetite or low compliance of those who were under the influence of a situation with strong psycho-emotional impact, own child suffering from cancer. Patients received food supplements with calcium, magnesium, vitamin D, omega, amino acids, vitamin C [32-35]. These recommendations are in compliance with international guidelines and literature [36]. Tailoring individualized oncology regimens requires analysis of gut microbiota by NGS.

It should be noted that one subject from the studied group underwent two HSCT procedures during the study, alloHSCT with graft failure which led to the second procedure, that of haploHSCT.

Among the limitations of the study, I mention: the impossibility of characterizing the gut microbiota before the application of the pre-HSCT conditioning treatment

in order to know the particular profile of the subjects (identification of taxonomic groups), the lack of determination of markers of digestive inflammation (calprotectin), the impossibility of applying a uniform diet, the applied treatments are similar, but not identical, low number of patients included. The main limitation, the lack of testing the gut microbiota by NGS, is in progress.

CONCLUSIONS

The identification of colonisations in the immunocompromised patient and the application of decontamination reduces the risk of infectious complications, but the refinement of the therapy by modulating the gut microbiota individualized per patient requires the analysis of the gut microbiota through NGS with a role in reducing the morbidity and mortality of these patients.

Acknowledgement

This article was published with the support granted by the project entitled "Net4SCIENCE: Applied doctoral and postdoctoral research network in the fields of smart specialization Health and Bioeconomy", project code POCU/993/6/13/154722.

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