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ANALYSIS OF THE DISTRIBUTION OF JAK2V617F MUTATION IN PATIENTS WITH CHRONIC MYELOPROLIFERATIVE NEOPLASMS TREATED AT THE HEMOAM FOUNDATION IN THE PERIOD 2017-2020

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Background: Chronic myeloproliferative neoplasms are a group of diseases that are characterized by hyperplasia of hematopoietic progenitor cells in the bone marrow and mature cells in the peripheral blood. According to the 2016 review by the World Health Organization, among the disorders included in this definition are polycythemia vera, essential thrombocythemia, primary myelofibrosis, chronic myeloid leukemia, chronic neutrophilic leukemia, chronic eosinophilic leukemia and unclassifiable myeloproliferative neoplasms. Standing out among those responsible for such clonal abnormality is the JAK2V617F mutation, which causes the constitutive activation of a tyrosine kinase, and leads to an overproduction of erythroid, myeloid and megakaryocytic elements that clinically predisposes patients to thrombosis, bleeding and leukemic transformation. This study aims to analyze the distribution of the JAK2V617F mutation in patients with chronic myeloproliferative neoplasms treated by the HEMOAM Foundation in the period 2017-2020. **Methods:** The molecular analysis of the JAK2V617F mutation was performed using polymerase chain reaction-restriction fragment length polymorphism (RFLP-PCR) and Sanger sequencing. Diagnostic parameters such as accuracy, sensibility, and specificity of the test were calculated using the online application OpenEpi. **Results:** A total of 103 samples were analyzed by RFLP-PCR methodology, 91 (88.3%) were negative, 12 (11.6%) were positive. Via Sanger sequencing, 8 samples (7.8%) carried the GT genotype (heterozygote) and 2 samples (1.9%) had the TT genotype (mutant homozygote), while 2 samples tested negative using this technique (GG). Thus, of the 12 samples previously classified as positive via the PCR-RFLP technique, 10 were positive for the mutation when tested using the Sanger method. The performance of the RFLP-PCR assay and Sanger sequencing for the detection of the JAK2V617F mutation showed equivalent results, with a level of diagnostic accuracy of 98.06%, sensitivity of 100% and specificity of 97.85%. **Conclusion:** The JAK2 genotyping of patients with MPNs is clinically useful and necessary for the service offered at HEMOAM. Both techniques can be used to detect the JAK2V617F mutation. RFLP-PCR can be used as a screening technique in laboratories where routine laboratory conditions are limited; and Sanger sequencing can be used in the diagnostic confirmation of the JAK2V617F mutation in myeloproliferative neoplasms.

Keywords: myeloproliferative neoplasms; Janus kinase; hematopoiesis; polymerase chain reaction; Sanger sequencing.
Financial support: FAPEAM and CNPq.

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NURSING ASSISTANCE IN CLINICAL HEMATOLOGY FOR PATIENTS WITH ACUTE TRANSFUSION REACTIONS

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Background: Blood transfusion is a procedure that consists of administering blood components and blood products to a patient with clinical and laboratory indications for transfusion. Performed by nursing professionals, the procedure is considered to be of low or medium complexity; however, it carries risks that involve from alloimmunization and viral infections in the immunological window to non-immunological reactions, including those that can lead to death. With the objective of exposing the complexities of hematology from a clinical point of view, the present work presents the experience of working in hemotherapy and dealing with its challenges in the face of transfusion reactions. **Methods**: Experience report of a nurse working with blood transfusions and conducting research in acute transfusion reactions in a blood center. **Results**: The act of transfusion is divided into three moments: pre, peri, and post-transfusion. Nursing assistance is responsible for installing and administering the blood component, accompanying the patient during the procedure, and intervening in the event of a reaction. In acute reactions, the transfusion is interrupted, and nursing interventions are performed on the patient, who may present clinical signs such as acute pain, dyspnea, fever, unstable blood pressure, itching and urticaria, nausea and vomiting, and ineffective tissue oxygenation, which may progress to a severe anaphylactic reaction and cardiorespiratory arrest. Despite the complexity of the presented picture, in many cases, doctors and nurses do not employ "patient blood management" in their clinical practices and still see transfusion as a simple volume replacement, and not as a transplant of hematopoietic tissue carrying donor antibodies, and possibly also viruses and bacteria, into the intravascular space of the recipient. **Conclusion:** It is of great importance to increase transfusion safety so that professionals who work in transfusion not only become aware of the care that is involved in the act of transfusion, but also understand the rational use of blood, keep themselves up to date in hemotherapy techniques and pay close attention to the risks involved in the procedure.

Keywords: hematology; hemotherapy service; blood transfusion; blood component transfusion; transfusion reaction.

Financial Support: FAPEAM.

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MOLECULAR PROFILE OF PATIENTS WITH CHRONIC MYELOID LEUKEMIA USING SECOND-LINE TYROSYKINASE INHIBITORS AT FHEMOAM

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Background: Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm with an incidence of 1-2 cases per 100,000 adults. Many studies on this disease have led to the possibility of effective diagnosis and treatments that together are able to molecularly control the disease through drugs called tyrosine kinase inhibitors (TKIs), which provide better rates of survival. One of the pioneering studies for the evaluation of TKIs, the IRIS, proposed a scale and subsequently other studies adopted it. In this way, monitoring was standardized on an international scale and the protocol of the European LeukemiaNet was established, which is currently one of the references for the diagnosis, treatment and monitoring of CML. The objective of this study was to evaluate the BCR-ABL1 transcripts using the qPCR method and demonstrate the molecular response profile of patients with CML treated with second-line tyrosine kinase inhibitors at Fundação Hospitalar de Hematologia e Hemoterapia do Estado do Amazonas (FHEMOAM). **Methods:** A retrospective survey of the results of BCR-ABL1 transcript tests, available in the medical records of patients with CML, was performed. **Results:** The data obtained from the study were analyzed according to the guidelines for molecular monitoring of the ELN. As such, it was identified that 6.3% have a sustainable major molecular response (RMMS), 41.7% a sustainable deep molecular response (RMPS), 8.4% have a major and unsustainable molecular response (RMM-NS), 6.3% a profound and unsustainable molecular response (RMP-NS), 25% have no molecular response (SR) and 12.5% did not undergo tests to perform the analysis. **Conclusion:** In view of the above and according to the literature, it was possible to establish a profile for identifying how many and which CML patients would be able to participate in the study. In addition, from this response profile, we evaluated which patients are actually committed to their treatment and which might benefit from a possible discontinuation of the drug in a future study.

Keywords: chronic myeloid leukemia Philadelphia chromosome; tyrosine kinase inhibitors; BCR-ABL.

Financial Support FAPEAM, FHEMOAM and CNPq.

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OUTCOMES OF PALLIATIVE CARE IN PATIENTS WITH ACUTE MYELOID LEUKEMIA IN END-OF-LIFE CARE: A REVIEW OF THE LITERATURE

Manuella Fonseca Benayon Cavalcanti Albano de Souza[1*]; Hitesh Babani[2]; Beatriz Oliveira Cardoso[1]; Giovana de Oliveira Sarubi[1]; Ádria Melissa Silva Campos[1]; Ornella Aquino da Silva[1]; Steffany Protásio Moura de Oliveira[1]; Marjorie Bindá Leite[1]; Caroline Souza dos anjos[1] & Monique Freire Santana[2];

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Background: Patients with acute myeloid leukemia receive intensive induction chemotherapy and face the abrupt onset of a life-threatening disease. These patients need to start urgent treatment with prolonged hospitalization for recovery, through which they experience physical symptoms at the expense of the effects of intensive chemotherapy, negatively impacting their quality of life. Facing psychological distress in the uncertainties about the prognosis, these patients need to discuss their preferences for optimal care. The aim of this study is to describe the outcomes of palliative care at the end of life of patients with acute leukemia. **Methods:** An integrative review of the literature was conducted via a survey in Pubmed, which selected papers published between 2012 and 2022, totaling 16 papers. Of these, 13 were used. **Results:** Palliative care interventions improved quality of life, symptom burden, and physical and mental symptoms, and patients were able to end their life with dignity. Palliative care needs to be based on multidisciplinary team management for end-stage patients with acute leukemia with the purpose of improving quality of life. In addition, the presence of a multidisciplinary team was associated with multiple positive results. Improving access to palliative care for people with acute leukemia might reduce their suffering and that of their loved ones. **Conclusion:** Palliative care is a multidisciplinary approach that focuses on communication, shared decision making, and advanced care planning. It also provides relief from pain and other distress symptoms, integrates psychological and spiritual aspects of care and supports families during illness and bereavement. The aim of the integral care approach is to evaluate the patient as a whole (spiritually, socially, physically, and emotionally). This study indicates that there are associations between palliative care and positive outcomes for end-of-life patients with acute myeloid leukemia.

Keywords: outcomes; palliative care; acute myeloid leukemia; end-of-life.

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IMMUNO-MOLECULAR PROFILE FOR PREDICTING PROGNOSIS IN PATIENTS WITH COLORECTAL CANCER

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Background: According to statistical data, colorectal cancer ranks second as the tumor with the highest incidence in Brazil. It is known that molecular biomarkers play an important role in the detection and management of patients with colorectal cancer. This review aims to verify the relevance of the correlation between biomarker expression and prognosis in patients with colorectal cancer. **Methods:** A integrative review of the literature was conducted via a survey in Pubmed, which selected papers published between 2015 and 2021, totaling 24 papers. Of these, 6 were used in the review. **Discussion:** Markers, such as Bcl-2 protein and human lymphocyte antigen (HLA) class I, are associated with a favorable prognosis; however, the sensitivity depends on the stage at which the neoplasm is currently at. Furthermore, the human epidermal growth factor II and III receptors (HER-2 and HER-3) regulate cancer cell proliferation and apoptosis. Therefore, overexpression of these biomarkers reveals poor prognosis and resistance to treatment with cetuximab. Nuclear factor kappa B (NF-kB) is also highlighted as a key marker for indicating a worse prognosis in patients with solid tumors. In counterpoint, the S100A4 protein represents a negative prognosis. **Conclusion:** It is understood that the integration of various biomarkers is needed in clinical-pathological applications with emphasis on optimizing treatment and better prognosis of these patients.

Keywords: colorectal cancer; molecular markers; immunohistochemistry; prognosis.

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SICKLE CELL TRAIT IN THE POPULATION OF THE BRAZILIAN AMAZON: GENETIC AND EPIDEMIOLOGICAL ANALYSIS

Marjorie Bindá Leite[1*]; Manuella Fonseca Benayon Cavalcanti Albano de Souza[1]; Ádria Melissa Silva Campos[1]; Steffany Protásio Moura de Oliveira[1] & Ornella Aquino da Silva[1];

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Background: Sickle cell anemia (SCA) is one of the most severe and common homozygous inherited genetic disorders in the world. This condition causes polymerized red blood cells, and compromises the body's functionality, leading to blood flow obstruction, hemolysis, and vaso-occlusion crises, which are somatized in a metabolic cascade that is responsible for the main clinical manifestations and expressive morbidity. This work aims to identify the main sickle cell genetic traits in the population of the Brazilian Amazon and determine the prevalence of the disease compared to other regions of the country. **Methodology:** An integrative literature review was developed in 3 steps: development of the research question, search for papers in the Pubmed database, and critical analysis of included papers. The investigation was conducted in September 2022, and papers between 2012 and 2022 were selected, totaling 69 papers, of which 10 were used in the review. **Results:** Sickle cell anemia is caused by a genetic alteration of multisystemic consequence, in which polymorphisms of genes that influence the immune response and that can modulate the severity of the disease, were identified. In addition to haplotypes, the most prevalent ones found were VCAM1, TGA2, MTHFR, IL4R, TNF-α, and TGF-ß. In the first months of life, SCA is asymptomatic due to the predominance of fetal Hb until 6 months of age and presents less aggressive symptoms. However, research showed that in 2015, in the state of Amazonas, elevated fetal hemoglobin concentrations were more frequent in women, evolving with cases of stroke, heart and kidney failure, and liver sequestration. According to data from the Brazilian Ministry of Health, the prevalence of sickle cell in the northern and northeastern regions was 6% to 10%, while in the southern and southeastern regions the prevalence is less than 2% to 3%. **Conclusion:** Sickle cell disease patients followed up in the state of Amazonas have a profile of clinical complications and alterations in laboratory exams that are compatible with that described in other populations in Brazil, despite a higher frequency of homozygotes. Epidemiological data in the state of Amazonas are still scarce, although some authors have tried to track this population diagnosed with sickle cell disease at the HEMOAM Foundation. It is also important to highlight the ethnic peculiarities of the population of the state of Amazonas in comparison with other populations.

Keywords: sickle cell; Amazon; epidemiology.

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UPDATE IN THE MANAGEMENT OF CHRONIC PAIN IN PATIENTS WITH MULTIPLE MYELOMA: A REVIEW OF THE LITERATURE

Denner Matheus Ribeiro Nascimento[1*]; Hitesh Babani[2]; Giovana de Oliveira Sarubi[1]; Kamyle Jade Rodrigues[1]; Beatriz Oliveira Cardoso[5]1]; Nabil Abuchahin[1]; Monique Freire Santana[1] & Hiochelson Najibe Ibiapina[3].

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Background: Multiple myeloma is a hematological malignancy with few treatment modalities, and often has difficult remission. Therefore, as it becomes chronic, it is important that health professionals distinguish the suffering from the unfavorable perspectives for improvement in affected patients. The aim of this paper is to identify the most effective interventions for chronic pain that will lead to a better quality of life for patients with multiple myeloma. **Methods:** A literature review was developed in three steps: development of the research question, search for papers in the Pubmed database and critical analysis of the included papers. The search was conducted in September 2022, and articles between 2012 and 2022 were selected, totaling 79 papers, of which 10 were used in the review. **Results:** Healthcare professionals who encourage patients to do personalized exercises and who perform chronic pain management correctly achieve more positive results regarding their functional capacity. In addition, patient and clinician education regarding the use of opioids, thalidomide, and lenalidomide decreases the risk of iatrogenesis. **Conclusion:** The multidisciplinary approach of physician, nurse, physiotherapist, and others if needed, coupled with accurate pain assessment and classification, provide safe treatment by selecting the right medication and exercise, with appropriate monitoring, for the myeloma patient.

Keywords: chronic pain; multiple myeloma; management.

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INFLUENCE OF MICROVESICLES ON INFLAMMATION, COAGULATION AND HOMEOSTASIS AFTER VIPERID SNAKEBITES

Kamille Beltrão Seixas[1,2]; Juliana Costa Ferreira Neves[1,2*]; Hiochelson Najibe dos Santos Ibiapina[1,2]; Jacqueline de Almeida Gonçalves Sachett [1,2]; Fábio Magalhães-Gama[3,4]; Andréa Monteiro Tarragô[4,5]; Marco Aurélio Sartim[1,2]; Adriana Malheiro[1,4,5,6]; Wuelton Marcelo Monteiro[1,2] & Allyson Guimarães da Costa[1,2,4,5,6]

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Background: Viperid venoms comprise a set of proteins and peptides that lead to a variety of toxic effects when released in the body. Some of these toxins are coagulants and can activate clotting factors, which act on the cascade and aggregation of platelets. Alterations in clotting and homeostasis are common signs after envenomation. The action of the venom components can lead to an increase in the concentration of microvesicles (MVs). MVs are derived from the cell membrane and participate in the regulation of the immune response. Thus, this review seeks to analyze data regarding the influence of microvesicles on inflammation, coagulation, and homeostasis after viperid snakebites. **Methods:** This review was based on 11 papers in the literature, all written in English and published between 2004 and 2019**. Results:** Cell-derived MVs are found in the circulation (erythrocytes, platelets, leukocytes, and endothelial cells). Flow cytometry is used to quantify MVs and determine their origin. Different immune cells are capable of releasing MVs, which act in the immune system as important paracrine messengers. The endothelium is one of the targets of the circulation of MVs, which are regulators of endothelial cells and participate in homeostasis through functions such as apoptosis, proliferation, migration, and inflammation. Coagulation and inflammation are linked and balanced biological systems. Tissue factor (TF) is the main activator of the coagulation cascade, being expressed in circulating MVs, which play a central role in the initiation of the coagulation cascade. MVs have been shown to accumulate during clot formation induced by cell injury and can lead to thrombosis. In a pathological state, MVs with active TF confer a predisposition to thrombotic events. Several studies suggest that alterations in MV concentrations after envenomation may indicate damage to the endovascular system that are generated by toxins. Furthermore, it is observed that MVs derived from red blood cells are elevated in patients after envenomation by a tiger snake. **Conclusion:** Studies show that a greater release of MVs as well as a high production of inflammatory mediators can usually be associated with the severity of pathological processes such as hemostatic disorders, inflammation, and dysfunction of endothelial function after viperid snakebites.
Keywords: envenomation, extracellular vesicles, immune response.

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ACCURACY OF THE CHEMILUMINESCENCE ASSAY COMPARED TO WESTERN BLOT TEST FOR HTLV-1 AND HTLV-2 DIAGNOSIS IN BLOOD DONORS OF AMAZON STATE

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Background: Human T-cell lymphotropic virus (HTLV) types 1 and 2 are retroviruses and may be associated with hematologic and neuropathologic malignancies. It is estimated that there may be more than 20 million infected people in the world, although most are asymptomatic carriers. However, regarding diagnosis, there are many gaps to be investigated and these gaps create difficulties in confirming infection by the virus. Chemiluminescent microparticle immunoassays (CMIA) are used in the screening of blood donors in Brazilian blood centers; however, it is necessary to confirm the infection using other methods such as western blot (WB) and PCR. Thus, the present study evaluated the accuracy of the CMIA compared to the WB test for confirming HTLV-1/2 infection in blood donors from the state of Amazonas. **Methods:** A cross-sectional study was conducted at Fundação Hospitalar de Hematologia e Hemoterapia do Amazonas. The population consisted of donors from January 2018 to December 2021 who were unfit for blood donation due to positive serology for HTLV. Participants were recruited and retested for CMIA and those with a positive result underwent WB testing. **Results:** 395 blood donors were identified with a positive result for HTLV via the CMIA. Of these, 142 (36%) returned to the HEMOAM to repeat the test, with a positive result being identified in only 77 (19%). Samples from these individuals were sent for WB testing, and HTLV-1/2 infection was confirmed in only 30 samples. Furthermore, 7 donors had an indeterminate result via WB. Regarding the diagnostic accuracy of CMIA, it was observed that the sensitivity was 100% (CI 95%: 89-100), specificity was 62% (CI 95%: 52-71) and accuracy was 70% (CI 95%: 62-77). **Conclusion:** Thus, we can see that the CMIA has an excellent sensitivity for screening blood donors with a positive result for HTLV-1/2; however, it has a low ability for confirming the infection. Nonetheless, future studies should be performed to demonstrate the diagnostic accuracy of the CMIA when compared to other methods.

Keywords: HTLV; chemiluminescence; western blot; sensitivity; specificity.

Financial Support: FAPEAM, CAPES and CNPq.

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RARE CASE OF FAMILIAL MYELOPROLIFERATIVE NEOPLASM IDENTIFIED IN PATIENTS AT THE HEMOAM FOUNDATION

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Background: Myeloproliferative neoplasms are clonal hematopoietic stem cell diseases characterized by hyperplasia of elements of the myeloid series. Essential thrombocythemia, polycythemia vera and myelofibrosis are the most frequent, and are differentiated by laboratory, clinical and genetic parameters. JAK2V617F (rs77375493; c.1849G>T) is responsible for most cases of these diseases, whereas inherited factors alter the risks at each stage of development of the disease. Hereditary predisposition is rare in myeloproliferative neoplasms, and is characterized by low penetrance, presence of somatic genetic variants, risk of progression to acute myeloid leukemia and its occurrence in two or more members of the same family. This study describes a rare case of familial myeloproliferative neoplasms identified among patients treated at the HEMOAM Foundation. **Methods**: Analysis of the medical records in the period 2021-2022 of patients who agreed to participate in the research. Clinical, laboratory data, hemorrhagic and thrombotic events, and mutational status of *JAK2V617F* were evaluated. **Results**: A family grouping was identified with three individuals (mother and two daughters) diagnosed with polycythemia vera: Patient A female, 78 years old, matriarch of the family, treated since 2018 when she had a hypotensive episode with transient cerebral ischemic crisis; in 2020, she was diagnosed with Alzheimer's, carries *JAK2V617F*, variant in heterozygosity (G/T), and is treated with therapeutic bleeding. Patient B female, 53 years old, treated at the HEMOAM Foundation since 2017; six months before diagnosis, she presented nighttime itching, blurred vision, holocranial headache, paresthesia, dizziness, syncope and vomiting; she is hysterectomized, had cysts laterally in the breast in 2017, she is hypertensive, also has gastritis and erosive duodenitis, and carries the *JAK2V617F* variant in heterozygosity (G/T); she has been treated with hydroxyurea and acetylsalicylic acid. Patient C 46 years old, female, treated at the foundation since 2016; she has a clinical diagnosis of Budd-Chiari syndrome, presented with splenomegaly in 2016, carries the *JAK2V617F* variant in homozygosity (T/T), undergoes therapeutic bleeding and takes hydroxyurea. **Conclusion**: the clinical and genetic findings are consistent with those described in the literature on familial myeloproliferative neoplasms. Investigating other molecular information for germline variants may help to understand the molecular landscape involved in familial cases of these diseases.
Keywords: heredity; bone marrow neoplasms; polycythemia vera; JAK2.

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THREE CASES OF MYELOPROLIFERATIVE NEOPLASMS IDENTIFIED BEFORE THE THIRD DECADE OF LIFE AMONG PATIENTS TREATED AT THE HEMOAM FOUNDATION

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Background: Myeloproliferative neoplasms are hematological diseases characterized by the overproduction of blood cells. Polycythemia vera, essential thrombocythemia and myelofibrosis are the most frequent *BCR-ABL1* negative myeloproliferative neoplasms (incidence: 0.3-4.0 cases per 100,000 individuals) and affect individuals between the fifth and seventh decades of life. It is believed that this age group is more affected due to the accumulation of somatic genetic variations in hematopoietic genes (*JAK2* and others) over the years. Cases of myeloproliferative neoplasms before the third decade of life are rare, and the causes of their development are still not fully understood. A history of hematologic malignancies in the family and the presence of germline variants are hypotheses. The present study describes cases of myeloproliferative neoplasms identified before the third decade of life among patients treated at the HEMOAM Foundation. **Method:** Analysis of the medical records in the period 2021-2022 of patients who agreed to participate in the research. Clinical data, bleeding and thrombotic events, and mutational status of the *JAK2V617F* variant were evaluated. Molecular analysis to identify the rs10974944 (C>G), a marker of the JAK2 46/1 haplotype, was performed usingSanger sequencing. **Results**: 109 patients were included in the study; 3 (2.7%) cases were identified before the third decade of life. Patient V.G.S, female, 21 years old, clinical diagnosis of essential thrombocythemia and hypermenorrhagia, under treatment with hydroxyurea. Patient L.P.S.S, 20 years old, clinical diagnosis of polycythemia vera, presented pulmonary arterial hypertension and does not receive treatment. Patient F.A.L, 23 years old, clinical diagnosis of essential thrombocythemia, hypermenorrhagia; has been treated with hydroxyurea and acetylsalicylic acid; has a history of other neoplasms in the family (mother has uterine cancer, uncle has lymphoma). All patients are negative for *JAK2V617F*, but only V.G.S and L.P.S.S were positive for haplotype 46/1 (genotype G/G and G/C, respectively) **Conclusion**: The cases identified in the sample universe demonstrate the rarity of juvenile cases. Absence of the *JAK2V617F* variant, the protagonist in the etiopathogenesis of these diseases, and presence of JAK2 46/1 haplotype, a risky germline variant, demonstrates the need to investigate other genes and germline variants involved in the pathogenesis of these cases.

Keywords: polycythemia vera; essential thrombocythemia; primary myelofibrosis; JAK2.

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EVALUATION OF IMMUNOPHENOTYPIC MARKERS USING FLOW CYTOMETRY FOR CLASSIFICATION OF ACUTE LYMPHOBLASTIC LEUKEMIA SUBTYPES IN AMAZONAS STATE, BRAZIL

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Background: The classification of leukemias is of great importance in therapy, and the classification of the subtype directly influences the clinical and therapeutic management. Flow cytometry allows the immunological identification of surface, cytoplasmic and nuclear antigens, thus enabling the detection of the affected lineage, the stage of maturation and the abnormal antigens expressed by the leukemic cells. As such, the objective of this study was to analyze the subtypes of acute lymphoblastic leukemia (ALL) and the markers detected through flow cytometry performed on samples from patients treated at Fundação Hospitalar de Hematologia e Hemoterapia do Amazonas (HEMOAM). **Methods:** A cross-sectional study was carried out from 2016 to 2021. The population consisted of patients treated at HEMOAM with a diagnosis of ALL. Data were obtained from medical records of the Medical and Statistical Care Sector, tabulated and analyzed using Microsoft Excel. **Results:** We identified 484 cases of ALL diagnosed in the years studied. The most common subtype observed through immunophenotypic markers was lineage B, with 89.90% (436) of the cases. From its subdivision, 412(84.95%) of the cases corresponded to intermediate/common B-ALL, followed by 11 (2.27%) cases of Pro-B-ALL, 7 (1.44%) of Pre-B-ALL, 3 (0.62%) of Mature B-ALL and 3 (0.62%) cases of common B-ALL Philadelphia$^+$. Lineage T had the lowest occurrence among the data found, with only 43 (8.87%). When subdivided, we observed 26 (5.36%) T-ALL cases for which subdivision data were not found, 8 (1.65%) cortical T-ALL cases, 6 (1.24%) cases of Early T ALL and 3 (0.62%) cases of Medullary T-ALL. No cases of Pro-T and Pre-T ALL were observed. However, 5 (1.03%) cases of acute biphenotypic leukemia were detected. **Conclusion:** The identification of ALL subtypes, such as common B-ALL Philadelphia$^+$ and Early T-ALL, proved to be important for initial stratification and for defining the clinical management to be used because these subtypes have a worse prognosis, with greater chances of having positive measurable residual disease at the end of remission chemotherapy.

Keywords: B-ALL; T-ALL; acute biphenotypic leukemia; immunophenotyping; flow cytometry.

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SENSITIVITY OF TECHNIQUES FOR DETECTION OF MEASURABLE RESIDUAL DISEASE IN ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: Acute lymphoblastic leukemia (ALL) is a hematologic malignancy that is characterized by the abnormal proliferation of leukemic blasts in the bone marrow, which are released into peripheral blood and extramedullary sites. Despite having a cure rate of 80-90% in developed countries, a significant number of patients still relapse. The relapse events in ALL may be related to the resistance of leukemic cells to chemotherapeutics, thus resulting in persistence after remission-inducing therapy and characterizing measurable residual disease (MRD). In addition, MRD can be defined as the presence of residual leukemic cells not detected by conventional methods. Thus, a literature review was performed to compare the techniques used for the evaluation of MRD in patients with ALL. **Methods:** The review was based on studies that evaluated the presence of MRD via three methods: 1) Morphological analysis and leukemic blast count using a myelogram; 2) Evaluation using flow cytometry; 3) Evaluation using real-time PCR. **Results:** The data demonstrated that the sensitivity of the myelogram by microscopy was $< 10^{-2}$, allowing the identification of 1 leukemic cell in up to 500 normal cells. In the analysis of immunophenotyping using flow cytometry, a sensitivity of 10^{-5} was observed, identifying 1 leukemic cell in the range of 10,000 to 100,000 normal cells. Finally, using real-time PCR, a sensitivity of 10^{-6} was observed, identifying 1 leukemic cell in the range of 100,000 to 1,000,000 normal cells. **Conclusion:** Thus, it was demonstrated that the best method for MRD evaluation was real-time PCR since it provided the highest sensitivity of the three. However, it is important to note that this technique has higher costs than the other two methods. In addition, flow cytometry presents itself as an effective alternative for MRD assessment. Of note, MRD monitoring via flow cytometry or real-time PCR has been used extensively in the follow-up and stratification of patients.
Keywords: leukemia; MRD; sensitivity; monitoring; follow-up.

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MAIN CARDIOTOXIC EVENTS IN THE FOLLOW-UP OF ONCO-HEMATOLOGIC PATIENTS

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Background: The improvement in the efficacy of antitumor agents in hematological malignancies has also brought a new problem, namely cardiotoxicity as an adverse effect. Chemotherapeutic drugs and other agents are widely used as the main therapies against leukemias, non-Hodkins lymphomas, and multiple myelomas. However, there are numerous cases of cardiotoxic effects of these drugs, which can be as deleterious as the neoplasm itself. This study aims to identify the main cardiotoxic consequences developed as a result of the treatment of hematological malignancies. **Methods:** An integrative review of the literature was conducted via a survey in Pubmed, selecting papers published between 2012 and 2022, totaling 21 papers. Of these, 7 were used in the review. **Results:** Studies report that the main antineoplastic agent used in onco-hematology, doxorubicin (a drug of the anthracycline class) has been associated with major adverse events, such as arrhythmias, myocarditis, pericarditis, and decreased LVEF of more than 10% of baseline, which is due to elevated expression of the TLR4 protein and increased transferrin levels in the blood. Besides DOXO, CAR T-cell therapy can cause serious acute effects, such as tachycardia with fever, hypotension, elevated troponin, pulmonary edema, a 25% decrease in LVEF, cardiogenic shock, QT interval prolongation, and atrial fibrillation. Despite this, strategies to prevent and reduce these cardiotoxicities without impairing the antineoplastic effects are already being studied. In this context, the use of drugs, such as metformin, empagliflozin, and i-SGLT2, used in the treatment of diabetes, may have protective effects against the adverse effects of anthracyclines. Furthermore, optimizing multidisciplinary team programs with cardiologists, oncologists, and hematologists is an emerging issue worldwide. **Conclusion:** The efficacy of antineoplastic regimens with anthracyclines for hematological neoplasms is undeniable. However, the clinical importance of cardiotoxic events during or after their use is also well known. In this sense, it is essential to expand access to early and constant cardiologic monitoring in these patients, increase the number of studies on new cardioprotection methods, and stimulate the partnership of professionals from multiple areas to reduce the impacts caused by hematologic malignancies and their treatment.

Keywords: cardiotoxicity; hematological neoplasms; therapy; clinical condition.

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PARTICIPATION OF MONOCYTES AND MACROPHAGES IN IMMUNE RESPONSE TO SARS-COV-2 VIRUS

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Background: SARS-COV-2 is the causative agent of the COVID-19 pandemic, which started in. It is an airborne virus that is capable of causing mild to severe symptoms, and which has a high mortality rate. The immune response is mainly guided by monocytes, which play a role in phagocytosis and the induction of the innate immune response. Since few studies have evaluated the participation of monocytes and macrophages on the acute phase during SARS-CoV-2 and subsequent convalescence, there is thus an urgent need to understand this participation. **Methods:** This is a narrative review that used the platforms Google Academic, PubMed and Scielo to locatepapers published between 2020 and 2022, in English, using the following descriptors: “SARS-COV-2”, “Monocytes”, “Macrophages”, “Acute infection”, “Convalescence”. Only original works were included. **Results:** Monocytes and macrophages can be infected by SARS-Cov-2 due to the expression of ACE-2. The acute phase is marked by the decrease in total monocyte count, though monocyte levels recover in convalescent phase. Acute conditions are marked by an increase in classical monocytes and a fall in intermediate and non-classical monocytes. It is known that these populations are involved in the production of inflammatory molecules, as well as acting on induction of the cytokine storm. In convalescence, there is a reestablishment in the levels of intermediate and non-classical monocytes, which demonstrates the tissue repair after the acute phase. M1-type macrophages are more susceptible to SARS-CoV-2 infection due to biochemical alterations that do not affect the integrity of the viral genetic material after phagocytosis, thus allowing its replication. On the other hand, M2-type macrophages are more resistant to infection, are induced by Th2 cytokines, and have a strong influence on IL-4/IL-13 axis. **Conclusion:** Both monocytes and macrophages actively participate in the response to infection by SARS-Cov-2, and are shown to be important, both for the worsening of the disease in the acute phase and for the restructuring of the tissue in the convalescent phase; however, more studies are needed to elucidate the role of these cells in COVID-19 and propose novel strategies of treatment.
Keywords: infection; inflammation; immune biomarker; COVID-19.

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FREQUENCY OF NATURAL KILLER T CELLS IN BONE MARROW AND PERIPHERAL BLOOD IN PATIENTS WITH B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA UNDERGOING INDUCTION THERAPY

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Background: Natural killer T cells correspond to a population of "unconventional" T cells that exhibit high antitumor activity. Studies suggest that, due to their cytotoxicity against tumor cells, there is an association between the antitumor function of natural killer T cells and antileukemic therapeutic treatments. Thus, the aim of the study was to evaluate the frequency of natural killer T cells in newly diagnosed pediatric patients with B-cell acute lymphoblastic leukemia who were undergoing treatment at the Fundação Hospitalar de Hematologia e Hemoterapia, in Manaus Amazonas, Brazil. **Methods:** This is an observational, longitudinal and prospective study in which bone marrow and peripheral blood samples were collected from ten pediatric patients with B-cell acute lymphoblastic leukemia at two moments of remission induction therapy, referred to as the day of diagnosis (D0) and end of remission induction therapy (D35). In parallel, immunophenotyping of natural killer T cells was performed using flow cytometry. The results were analyzed using the FlowJo software (v9.4), and statistical analysis and graphing were performed using GraphPad Prism (v8.2). **Results:** Our results demonstrated a significant decrease in the neutrophils, platelets and hemoglobin on D0 in the patients with B-cell acute lymphoblastic leukemia when compared to the control group. Furthermore, we observed an increase in the frequency of natural killer T cells in the peripheral blood of the patients on D0 when compared to the control group ($p<0.001$). In addition, when evaluating the kinetics during remission induction therapy, we observed a decrease in these cells on D35 ($p<0.001$), which was also observed in the bone marrow. Interestingly, the increase in the frequency of natural killer T cells on D0 may be related to the number of leukemic blasts in the blood marrow of pediatric patients on D0 (75%]). **Conclusion:** Additional studies that evaluate the frequency of natural killer T cells at other times of remission chemotherapy, as well as their association with the clinical prognosis in patients with B-cell acute lymphoblastic leukemia, are needed.

Keywords: childhood leukemia; unconventional T cells; tumor microenvironment; flow cytometry; prognosis.

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IMMUNOLOGICAL ROLE OF MYELOID CELLS IN THE LEUKEMIC MICROENVIRONMENT AND THEIR CLINICAL IMPLICATIONS

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Background: Myeloid cell subpopulations correspond to a heterogeneous group of innate immune cells that include tumor-associated neutrophils (TANs), tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs). In the context of leukemias, the mechanism by which leukemic cells induce the expansion and recruitment of these cells is still poorly described. Collectively, they can be abundant in different tissues and their presence in the leukemic microenvironment transcends the leukemia subtype and can significantly impact the clinical outcome, acting in a dichotomic manner and contributing to leukemic progression or stimulating antitumor responses. Therefore, this study aimed to describe the immunological role of myeloid cell subpopulations in leukemias. **Methods:** For this study, we performed a comprehensive review based on 149 papers that analyze the subpopulations of TANs, TAMs, and MDSCs and their participation in different types of acute or chronic leukemia. **Results:** The data from the literature demonstrated that a high number of neutrophils and macrophages exhibit a pro-tumor phenotype (N2-TANs and M2-TAMs, respectively), along with polymorphonuclear MDSCs (PMN-MDSCs) and monocytic MDSCs (M-MDSCs). These cells have a strong immunosuppressive activity via the production of anti-inflammatory mediators and the formation of leukemic niches, thus contributing to increased tumor burden. In contrast, the antitumor phenotype of these cells (N1-TANs and M1-TAMs, respectively) correlates with protective functions via the release of cytotoxic mediators, tumor antigen presentation, induction of apoptosis, and phagocytosis. Additionally, several studies highlight the role of these cell populations as critical determinants for resistance to chemoimmunotherapy and targeted therapies and they can even serve as a treatment evaluation parameter. **Conclusion:** Collectively, it is noted that most studies indicate that the presence of myeloid cells is associated with an increased leukemic burden and, consequently, a poor prognosis. Thus, the reprogramming or repolarization of myeloid cells presents itself as a promising strategy that can be explored in the context of immunotherapeutic approaches targeting leukemias.
Keywords: leukemia; neutrophils; macrophages; myeloid-derived suppressor cells; immune response.

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ASSOCIATION OF SERUM LEVELS OF MANNOSE-BINDING LECTIN WITH THE SUSCEPTIBILITY OF INFECTIONS IN PEDIATRIC PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

Júlia dos Santos Moraes[1*]; Fábio Magalhães-Gama[1,2]; Mateus de Souza Barros[1,3]; Flavio Souza da Silva[1,3]; Izabela Cabral de Freitas[1]; Fabíola Silva Alves Hanna[1,3]; Andréa Monteiro Tarragô[1,3,4]; Nilberto Dias de Araújo[1,3,4]; Adriana Malheiro Alle Marie[1,3,4] & Allyson Guimarães da Costa[1,3,4]

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Background: Mannose-binding lectin (MBL) is an innate immune molecule that activates the lectin complement pathway of the complement system by recognizing carbohydrates on the microbial surface, thus contributing to the opsonization, lysis and phagocytic killing of the invading microorganism. Studies indicate that there is an association between serum MBL levels and an increased risk of infections in pediatric patients with acute lymphoblastic leukemia (ALL) during chemotherapy, which contributes to morbidity and mortality. Thus, the study aimed to describe the role of MBL in the early identification of patients at higher risk of infections during chemotherapy. **Methods:** This review was based on ten papers published since 2009 on the association of serum MBL levels with the risk of infections in pediatric patients with ALL. Among the ten selected papers, eight of these were used in the review. The techniques used in the papers were ELISA and real-time PCR to analyze serum levels and MBL polymorphisms, respectively. **Results:** The studies demonstrate that, based on serum MBL levels, pediatric patients undergoing treatment can be divided into two groups: patients with normal MBL or MBL-deficient patients and, for the second group, it is observed that the deficiency in the levels of MBL can be caused by a polymorphism in the gene MBL2, which contributes to a greater risk of infections. Some studies have also correlated low levels of MBL with the development of sepsis, which may be due to a possible interaction between pro-inflammatory cytokines, coagulation and complement molecules. In addition, recent studies indicate that low levels of MBL may serve as possible biomarkers that predict viral infections and death in patients undergoing allogeneic stem-cell transplantation. On the other hand, normal or elevated levels of MBL are associated with a shorter duration of episodes of febrile neutropenia in the first two years after diagnosis. It is worth noting that other studies have not observed a significant association between serum MBL and prognosis. **Conclusion:** The data demonstrated that low levels of MBL are associated with a worse prognosis in patients with ALL. However, the role of serum MBL as a biomarker still needs to be further explored.
Keywords: lectin complement pathway; complement activation; childhood leukemia.

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ANALYSIS OF THE FREQUENCY OF BONE MARROW- AND PERIPHERAL BLOOD-DERIVED γδ T CELLS IN PEDIATRIC B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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Background: B-cell acute lymphoblastic leukemia (B-ALL) represents the most frequent cancer type in childhood. The leukemic burden in bone marrow (BM) and its release in peripheral blood (PB) results in an effector T cell mobilization that contributes to disease control. While classical T cells are strongly affected by the disease, lymphocytes, such as gamma-delta (γδ) T cells, exhibit higher cytotoxicity and less exhaustion, but their functional and prognostic value in B-ALL remains elusive. Thus, this study aimed to evaluate the frequency of γδT cells in children with B-ALL. **Methods:** In this study, BM and PB samples were collected from 10 children (6 males and 4 females; median age=6 years; IQR=3-8) diagnosed with B-ALL, during two-time points referred to as the day of diagnosis (D0) and the end of remission chemotherapy (D35). To constitute a control group (CG), 10 healthy children (5 males and 5 females; median age=9 years; IQR=6-13) were recruited and only PB was collected. The analysis of γδT cell frequency was performed using flow cytometry. The results were analyzed using FlowJo software (v9.4), and statistical analysis and graphing were performed using GraphPad Prism (v8.2). **Results:** We observed that, on D0, γδT cells were more frequent in PB than in BM in the B-ALL patients, although no statistical significance was observed ($p=0.0928$). Furthermore, it was observed that γδT cells were significantly more frequent in the PB of the B-ALL patients compared to the CG ($p<0.0001$) on D0. In a side-by-side analysis between the BM and PB compartments on D0 and D35, it was observed that the frequency of γδT cells in both the BM ($p=0.0465$) and PB ($p=0.0371$) was higher on D0, but decreased on D35. **Conclusion:** We demonstrated that γδT cells are affected in B-ALL. Our data indicate that these T cells expand in response to the tumor development and tend to decrease at the end of chemotherapy, and it seems that the leukemic burden is controlled after treatment, thus indicating a possible immune response. Further studies will be needed to understand the kinetics of these T cells and their prognostic value in the context of B-ALL.

Keywords: B-cell acute lymphoblastic leukemia, gamma-delta T cells, tumor microenvironment, immunosurveillance.

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INFLAMMATION AFTER *BOTHROPS* SNAKEBITE AND ITS INFLUENCE ON THE PATHOGENESIS OF ACUTE KIDNEY INJURY

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Background: In the Brazilian Amazon, snakebites by *Bothrops atrox* are the most common cause of envenomations. *B. atrox* venom can cause systemic pathophysiological alterations such as acute kidney injury (AKI). Studies indicate that acute inflammation after *Bothrops* sp. may play a role in the initiation and extension of AKI. This review analyzes the literature on inflammatory molecules released after the snakebite by *Bothrops sp* and their participation in AKI. **Methods:** This review was based on 18 papers, written in English, between 2004 and 2019. **Results:** *Bothrops sp.* venom can induce the elevation of molecules such as CXCL-9, IL-6, IL-2, IL -10, IL-17A, TNF-α, IL-6, IL-10, IFN-γ; in addition, the toxins present in the venom can produce molecules that induce inflammatory alterations. Renal vascular endothelium cells initiate early inflammatory responses in the injured kidney due to direct contact with the toxins, whereby renal cells exposed to the venom mimic the changes in the human body and, in response, produce mediators, such as chemokines and cytokines, that stimulate the migration of inflammatory cells to the kidney. In the first hours after envenomation, mainly neutrophils participate, which are followed by monocytes, with the involvement of endogenous mediators that lead to macrophage activation and regulate the production of cytokines. The CXCL-8 molecule presents a chemoattractant effect for neutrophils, and is related to proteinuria associated with kidney disease. In addition, CCL-2 has been cited as an important mediator in the process of kidney injury, and appears in high concentrations in kidney tissues of patients with glomerular diseases, and is associated with the infiltration of macrophages/monocytes in the kidneys. In addition, studies have demonstrated that venom fractions may be responsible for direct injury to kidney cells, with enzymes of proteolytic activity inducing the destruction of kidney structures through the generation of free radicals, activation, and release of mediators such as chemokines, cytokines and prostaglandins, among others. **Conclusion:** Soluble immune molecules has been correlated with the development of AKI after *Bothrops* sp. envenomation and may serve as predictive markers of this complication. Immune soluble mediators and immune cells may be important in renal pathophysiology after *Bothrops* envenomation.
Keywords: chemokines; cytokines, immune cells; kidney injury; inflammation.

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NEUTROPHIL TO LYMPHOCYTE RATIO AS A POSSIBLE PREDICTOR OF SEVERE TISSUE COMPLICATION IN *BOTHROPS* SNAKEBITES

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Background: Snakebites by *Bothrops sp.* represent a severe public health problem in the Brazilian Amazon. Tissue damage is an important clinical manifestation of these envenomations and can result in severe tissue complication (STC). In some cases, such damage can lead to sequelae in patients that generate significant social and economic impacts. In addition to the distinctive clinical manifestations, alterations in laboratory markers can serve as an indication of the severity local lesions and help to monitor the patients' evolution. Therefore, we evaluated the relationship between laboratory alterations and the development of STC in *Bothrops* sp. snakebite victims. **Methods:** The study involved 21 individuals who underwent biopsy of the local tissue lesion and had records of laboratory tests at admission, on the day of the biopsy, or 24 hours before this procedure. These patients were divided into 2 groups (STC^+ and STC^-) according with development of severe tissue complication. The Shapiro-Wilk test was used to verify the normality of the variables. Student's t test, a paired Wilcoxon test and a Mann-Whitney U test were used according to the distribution and normality of the variables. $P<0.05$ was considered significant. **Results:** Most snakebites occurred in males (76%), in rural areas (90%), with lower limbs being the most affected and 10 (48%) patients evolved with STC resulting from the envenomation. Between admission and the day of the biopsy, alterations in erythrocytes (p=0.0009), hemoglobin (p=0.0018), hematocrit (p=0.0021), white blood cells (p=0.0069), (p=0.0067), neutrophil to lymphocyte ratio (NLR) (p=0.0268), platelets (0.0006) and c-reactive protein (CRP) (p=0.0156) were observed in all patients. On admission, STC^+ patients showed an increase in total (p=0.0057), segmented (p=0.0012) and NLR (p=0.0001) leukocytes in relation to the STC^- group. On the day of biopsy, erythrocytes (0.004), hemoglobin (0.003) and hematocrit (0.003) were decreased, and there was an increase in CRP levels (p=0.0322) in STC^+patients. **Conclusion:** The NLR showed a constant and significant increase in patients who evolved with local complications and the use of this measure on admission of patients can help in predicting the prognosis of patients and in the better management of these individuals.
Keywords: snakebite; *Bothrops*; tissue damage; laboratory markers.

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CONDITIONED MEDIUM FROM MACROPHAGES PRE-TREATED WITH MCF-7 SECRETOME INCREASE CANCER CELL METABOLISM

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Background: The tumor microenvironment is characterized by a dynamic and complex relationship between cancer and non-cancer cells such as tumor-associated macrophages. Cell-cell communication is guided by the arrangement of macromolecules released by cells into the extracellular environment, and influences the progression of tumor cells. The aim of this study was to explore the effect of a breast cancer cell conditioned medium and induced macrophages treated with cancer cell secretome on cell viability and reactive oxygen species levels. **Methods** THP-1 monocytes were differentiated into macrophages using phorbol 12-myristate 13-acetate. The effect of a different proportion of conditioned medium (100%, 75%, 50% and 25%) generated in MCF-7 (estrogen receptor and progesterone positive cell line) and MDA-MB 231 (triple negative cell line) breast cancer cells on macrophages was determined at 48 h. In parallel, the secretome modulation of induced macrophages, previously treated with conditioned medium from MCF-7, was performed. For cell viability, the resazurin metabolization assay was performed and the reactive oxygen species levels were determined using the 2,7-dichlorodihydrofluoroscein diacetate protocol. Results were expressed as a mean ± standard error, and compared through analysis of variance (one-way) and Tukey's multiple comparison tests. **Results:** Macrophages treated with both breast cancer secretomes exhibited a decrease in cell viability and reactive oxygen species levels. Furthermore, MCF-7 cultivated with the secretome of pre-treated macrophages showed increases in reactive oxygen species levels and cell viability. **Conclusion:** The secretome generated from tumor cells modulated macrophages to burst the metabolism of tumor cells. Therefore, more experiments are required to better elucidate the cross-communication between cancer cells and macrophages.
Keywords: tumor microenvironment; cell viability; secretome; macrophages.

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IMPACT OF BONE MINERAL DYSFUNCTION ON CELL EXHAUSTION OF T LYMPHOCYTES IN PEOPLE LIVING WITH HIV/AIDS RECEIVING ANTIRETROVIRAL TREATMENT

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Introduction: Cellular senescence naturally accompanies aging, and this scenario, added to the dysfunction of bone mineral density, can be caused by several factors such as prolonged use of active antiretroviral therapy and the chronification of infection. For this reason, we intended to define the epidemiological profile of immunosenescence in people living with HIV who receive antiretroviral treatment and who have mineral bone disorder. **Methodology:** We performed a cross-sectional study with 30 people over 40 years old living with HIV with indetectable viral load due to long-term antiretroviral therapy, treated at the Fundação de Medicina Tropical Dr. Heitor Vieira Dourado (a tertiary center for tropical diseases) from August 1st, 2021 to March 30th, 2022. The samples were collected in heparin and EDTA tubes, the next step was isolation of human peripheral blood mononuclear cells (PBMCs) and immunophenotyping with antibody panels (CD4/CD8/CD3/CTLA-4/PD-1/CD45RO/HLA-DR) for the cytometry analysis. The patients were referred for bone densitometry that analyzed lumbar spine and femoral neck bone mineral density (BMD). **Results:** 30 samples of people living with HIV with osteopenia (T-Score of -1.0 to -2.4 standard deviation) were obtained, which came from 12 women and 18 men with a median age of 60 years and a median antiretroviral therapy time of 12 years. Average $CD4^+$ was of 500 cells/mm^3 and a CD4/CD8 ratio was less than 1. The immunophenotype indicated three exhausted phenotypes. The subpopulations ($CD3^+CD4^+CTLA\text{-}4^+$/CD45RO), ($CD3^+CD8^+PD\text{-}1^+$/CD45RO) and ($CD3^+CD4^+CTLA\text{-}4^+$/CD45RO/HLA-DR) showed a negative correlation with the T-score femoral neck BMD ($p= 0.0084/r^2= 0.36$), ($p= 0.0176/r^2= 0.25$) and ($p= 0.0211/r^2= 0.2899$) respectively. These phenotypes may be related to the to immunosenescence in people living with HIV/AIDS, and high expression of HLA-DR is related to the progression of the disease. **Conclusions:** From the three phenotypes ($CD3^+CD4^+CTLA\text{-}4^+$/CD45RO), ($CD3^+CD8^+PD\text{-}1^+$/CD45RO) and ($CD3^+CD4^+CTLA\text{-}4^+$/CD45RO/HLA-DR), we observed an association between cellular exhaustion and mineral bone disorder.
Keywords: mineral bone disorder; cell exhaustion; T lymphocytes; people living with HIV/AIDS.

Financing: CNPq and CAPES.

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ASSOCIATION OF MICRONUCLEI IN LEUKOCYTES OF PATIENTS TREATED WITH CONVENTIONAL TREATMENT FOR CUTANEOUS LEISHMANIASIS

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Introduction: Leishmaniasis is a pathology that annually affects about 1.5 million people spread across 88 countries on four continents. This infection has an increasingly wide geographic distribution, with cases in areas that were not previously considered endemic. Despite great advances in research in the areas of cell biology and immunology focused on this pathology, drug treatment has not been improved in a similar proportion, with few therapeutic alternatives currently available on the market. Even after 90 years, antimony-based solutions are still the drugs of choice for the treatment of leishmaniasis. In Brazil, the drug of medical preference continues to be Glucantime®; however, this drug has toxicological effects that cause adverse effects, such as the development of scientifically proven hepatitis and heart disease. Few studies have been carried out to analyze toxic effects related to genetic material. As such, this study aims to detect genotoxic and mutagenic effects in patients after exposure to treatment by Glucantime®, and identify whether there are structural changes to their genetic material. **Methodology:** 10 slides were prepared from peripheral blood collected by venipuncture of patients diagnosed with cutaneous leishmaniasis. Of these, five were from patients treated with Glucantime®, and five from untreated patients considered as a control group. These slides were fixed and later stained with Giemsa for further observation under an optical microscope at 1000X magnification. **Results and Discussion:** The microscopic analysis of the patient's slides before and after treatment with Glucantime® did not allow us to evaluate the association related to conventional treatment for cutaneous leishmaniasis with the presence of micronuclei in leukocytes of these individuals. Both groups of patients had micronuclei in their leukocyte cells. 40% of the patients who were not exposed to conventional treatment had micronuclei formation and 60% of the patients exposed to treatment also had micronuclei formation. **Conclusions:** This study showed that both the patients exposed to treatment with the antimonial Glucantime® and the untreated patients undergo cellular alterations, i.e., the formation of micronuclei, and this phenomenon cannot be associated with the use of this drug used in the treatment of cutaneous leishmaniasis.

Keywords: micronuclei; Glucantime; leishmaniasis.

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CHEMICAL CHARACTERIZATION AND *IN VITRO* CELLULAR ACTIVITIES OF *CROTON CAJUCARA* BENTH ESSENTIAL OIL-LOADED NANOPARTICLES

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Background: The essential oil obtained from *Croton cajucara* Benth has already been cited as having pharmacological applications; however, its biologic effects have not been well described. Lipid carriers are a form of drug delivery that allows prolonged release at the target site, solubilizing lipophilic compounds and reducing their toxicity. Thus, the objective of this work was to characterize the metabolites present in *C. cajucara* essential oil and evaluate the cellular morphology and viability of nanostructured lipid carriers loaded with *C. cajucara* oil. **Methods:** The chemical characterization of *C. cajucara* oil was performed using gas chromatography coupled to a mass spectrometer. The cell lines used in this study were A549 and BEAS-2B and THP-1 monocytes differentiated into macrophages using phorbol 12-myristate 13-acetate. The cell viability was determined via a resazurin metabolism assay after 24 hours of treatment with *C. cajucara*-loaded nanoparticles, blank nanoparticles, triglycerides-loaded nanoparticles, and *C. cajucara* oils and unencapsulated oils. The half-maximal inhibitory concentration was determined from non-linear regression curves. **Results:** The chemical characterization of the *C. cajucara* oil showed 22 metabolites, with the most abundant being linalool and 5-hydroxycalamenene. The half maximal inhibitory concentration value was obtained for all treatments and showed a similar pattern in different cell lines. The *C. cajucara* oil was more cytotoxic than the 100 µg/mL *C. cajucara*-loaded nanoparticle. In a low concentration, the *C. cajucara* oil increased the cancer cell proliferation and altered the cell morphology to a mesenchymal profile. **Conclusion:** The cell viability of pulmonary cell lines was affected in a dose-dependent manner. Encapsulation by nanoparticles reduced the cytotoxicity of *C. cajucara* oil. The major metabolites identified may be responsible for the anti-inflammatory and antioxidant activities of *C. cajucara* oil. Therefore, further studies will be necessary to expand the cell effects of this Amazonian plant.

Keywords: *Croton cajucara* Benth; nanotechnology; essential oil; cell viability.

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SECRETOME FROM MACROPHAGES PRE-TREATED WITH SECONDARY METABOLITES OF *PAULLINIA CUPANA* KUNTH REDUCE TUMOUR CELL VIABILITY

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Background: The tumor microenvironment consists of tumor cells and stromal cells, and includes immune system cells that regulate essential tumor survival and promotion functions. The secondary metabolites of medicinal plants have already related to modulation of the tumor microenvironment. *Paullinia cupana* Kunth, also known as guarana, has high concentrations of methylxanthines and epicatechins, and the immunomodulatory and antineoplastic activities of guarana have already been reported. The aim of this study was to evaluate the modulatory effect of tumor microenvironment cells pretreated with hydroalcoholic extract of guarana and its secondary metabolites on cancer lung cell viability. **Methods:** Viability assays were performed with resazurin on THP-1 differentiated into macrophages with phorbol 12-myristate 13-acetate, and BEAS-2B normal lung epithelial cells were treated with hydroalcoholic extract of guarana and isolated secondary metabolites (caffeine, theobromine, and epicatechin) to reach the half-maximal inhibitory concentration. Cells were treated with non-cytotoxic concentrations of guarana extract and its metabolites to generate the conditioned medium. These secretomes were collected and used to evaluate inhibition of the viability of A549, a lung cancer cell line. **Results:** The half-maximal inhibitory concentrations for the BEAS 2-B cell line were 24.0 (±0.02) mM for caffeine, 8.00 (±0.39) mM for theobromine, 0.17 (±0.01) mM for epigallocatechin gallate, and 3.44 (±11.11) mg/ml for the hydroalcoholic extract of guarana. In the macrophages, the values were 23.2 (±0.01) mM for caffeine, 4.00 (±0.20) mM for theobromine, 0.15 (±0.97) mM for epigallocatechin gallate, and 4.34 (±15.95) mg/ml for the hydroalcoholic guarana extract. Conditioned media from macrophages pretreated with caffeine and guarana extract reduced the cancer cell viability. However, conditioned media from BEAS-2B cells pretreated with guarana and its isolated metabolites caused no change in A549 cell viability. **Conclusion:** These findings indicate that the modulation of tumor microenvironment cells, such as immune and stromal cells, can be triggered by secondary metabolites of guarana. Further experiments will clarify the signaling pathway activated by the secretome generated in methylxanthine modulated cells.
Keywords: tumor microenvironment; guarana; secondary metabolites; methylxanthines; epicatechins.

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PSYCHONEUROIMMUNOLOGY: A LINK BETWEEN DEPRESSIVE DISORDER AND THE IMMUNE SYSTEM

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Introduction: Major depressive disorder is one of the most common neuropsychiatric diseases and has high rates of morbidity and mortality. It is characterized by changes in mood (sadness and loss of interest), volition (altered appetite and indisposition) and in the sleep-wake cycle (insomnia/hypersomnia). The influence of inflammatory cytokines on human behavior is already known and it produces symptoms that are very similar to those of depression, i.e., sickness behavior. The objective of our work is to map the relationship between cytokines, human behavior and depressive disorder. **Methodology:** This is an integrative literature review, which was carried out via an active search in the databases PUBMED, EMBASE, ISI Web of Knowledge, and PsychInfo, using the following descriptors: cytokines; depression; illness behavior; sickness behavior, psychoneuroimmunology. The selection of papers was performed by at least two authors, who also selected and extracted the data of the included papers. Articles in English and Portuguese that were available in full in the last 5 years were included. **Results:** During an infection, non-specific symptoms that arise, such as fever, reduced appetite, loss of interest, weakness, generalized malaise, apathy, difficulty concentrating, lethargy and reduced volition, are related to the action of pro-inflammatory cytokines such as interleukin-1, interleukin-6, interferons and alpha tumor necrosis factor. Due to the similarity of these symptoms (sickness behavior) with those of depression, several researchers have sought the correlation between the action of these cytokines in the brain and depression. Experiments conducted in animal model and in humans have shown that systemic and cerebral infusion of inflammatory cytokines and molecular patterns associated with pathogens (PAMPS), such as lipopolysaccharides (LPS), produce consistent changes in behavior patterns and can produce depressive symptoms. Another line of research lies in the genes that encode cytokines, such as interleukin-1, in the brain, and which are deregulated in depression. **Conclusion:** Although many studies have shown that cytokines produce sickness behavior, their role in the production of the depressive disorder is not clear, likewise factors such as genetic predisposition, neurodegeneration and stress arise as possible etiopathogenic factors. Whether cytokines aggravate depressive disorders is an open field to be researched in psychoneuroimmunology.
Keywords: cytokines; depression; illness behavior; psychoneuroimmunology.

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ANTILEUKEMIC ACTIVITY OF A PHOSPHINE COMPLEX OF RUTHENIUM

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Introduction: Acute myeloid leukemia (AML) is characterized by clonal expansion of immature myeloid blasts. In the state of Amazonas, AML has a high incidence rate and conventional treatment alternatives are limited. In addition to its sensitivity to chemotherapy, which causes toxic side effects in normal cells, it also causes multidrug resistance (MDR), which is one of the most critical problems in chemotherapy. Bioprospection of natural molecules can provide potential sources for the development of new drugs for chemoprevention or chemotherapy. Due to the biodiversity and availability of natural biomolecules, the Institute of Organic Chemistry and National Academy of Sciences of Ukraine has a growing interest in developing and evaluating the anticancer potential of natural and synthetic compounds. Therefore, the present study aimed to investigate the antileukemic activity of a phosphine complex of ruthenium. **Methods:** The cytotoxic activity of the compound was verified via an MTT assay. HL-60 and Vero cells were treated with different concentrations of phosphine complex of ruthenium over a 24-72 h period. In a continuation of the study, the role of the compound in the clonogenicity of HL-60 cells was investigated. Colonies were detected after 9 days of culture with the addition of MTT reagent (1 mg/ml). All experiments were performed in triplicate. **Results:** The phosphine complex of ruthenium showed a significant antileukemic effect against HL-60 cells. When non-linear regression was performed, it presented an IC_{50} value of 19.20 μM and no significant cytotoxic effect was observed against non-cancerous cell lines, such as Vero cells and human PBMCs. In addition, the compound tested was able to significantly inhibit the clonogenic growth when compared with untreated cells ($p < 0.05$). **Conclusion:** These data demonstrate that the phosphine complex of ruthenium has antileukemic potential, which can be pharmaceutically explored in future *in vivo* studies to better characterize its anticancer activity.

Keywords: leukemia; HL-60 cells; cytotoxicity activity; phosphine complex of ruthenium; bioactive compounds anticancer.

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CHARACTERIZATION OF CELL-DERIVED MICROVESICLE PROFILE IN PEDIATRIC PATIENTS WITH B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA UNDERGOING INDUCTION THERAPY

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Introduction: Microvesicles (MVs) correspond to a heterogeneous group of vesicles derived from plasma membrane, and are released by normal and cancer cells. Their presence in biological fluids may be associated with the severity of pathological processes, and their role as potential disease biomarkers and therapeutic targets has been highlighted. By analyzing 20 pediatric patients with B-cell acute lymphoblastic leukemia (B-ALL) during three moments of the induction therapy, referred to as day of diagnosis (D0), fifteenth day of induction therapy (D15) and the end of the induction therapy (D35), we seek to characterize the profile of cell-derived MVs in the bone marrow (BM), plasma and peripheral blood (PB). **Methodology:** MVs were measured using flow cytometry and labeled for specific cell markers of CD45 (leukocytes), CD66b (neutrophils), CD14 (monocytes), CD3 (T lymphocytes), CD19 (B lymphocytes), CD41a (platelets), CD235a (erythrocytes), CD51 (endothelial cells) and CD10, CD19 and CD34 (leukemic cells - LCs). Comparative analyses between B-ALL patients and the control group were carried out using a non-parametric Mann-Whitney test. Comparisons between the time points of induction therapy were performed using a Wilcoxon matched-pairs signed-rank test. In all cases, significance was considered at $p<0.05$. **Results:** The data demonstrated that B-ALL patients had a significant decrease in the MV levels derived from T lymphocytes and platelets when compared to the control group. On the other hand, an increase in MVs derived from endothelial cells in PB was observed, together with a notable increase in MVs from LCs with $CD10^+$ phenotype in BM and PB. The evaluation of the kinetics of circulating MVs during induction therapy demonstrated a decline in MVs from LCs $CD10^+$ in BM and PB, and MVs $CD19^+$ in PB on D35. Furthermore, a significant increase in MVs levels derived from platelets on D35 was observed. **Conclusion:** Our data indicates that: (I) B-ALL patients had a marked production of MVs derived from endothelial cells; (II) CD10 and CD19 were the most expressed markers in MVs derived from LCs; and (III) MVs derived from LCs may reflect the leukemic blast quantity in B-ALL.
Keywords: childhood leukemia; extracellular vesicles; leukemic microenvironment biomarkers; flow cytometry.

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THE ROLE OF EXOSOMES IN CANCER VACCINE DEVELOPMENT: INSIGHTS AND NEW PERSPECTIVES

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Introduction: Cancer is a leading cause of death worldwide and cases are projected to continue increasing as life expectancy increases. Although patient survival rates for some forms of cancers are high due to clinical advances in treatment, the search for effective cancer vaccines remains necessary. In this context, approaches based on nanometric vesicles, named exosomes (EXO), have emerged as attractive targets due to their biological activities and potential therapeutic applications. This work aimed to describe the application of EXO derived from tumor cells (TEX), dendritic cells (DEX), and cytotoxic T lymphocytes (CTL-EXO) as cancer vaccines, as well as the challenges and future directions associated with their application. **Methodology:** This review considered preclinical and clinical studies present in the literature on EXO-based immunotherapeutic vaccines. **Results:** TEX contain antigens associated with the tumor that can be presented directly on the surface of cancer cells or via antigen-presenting cells of the recipient, which triggers an immune response against the tumor. DEX retain crucial immune stimulating properties of its mother cell, and are able to present antigens to T cells directly or indirectly. DEX carry peptide/major histocompatibility complex class I or class II complexes (including specific tumor peptides) and a variety of co-stimulatory molecules, which enable responses of helper and cytotoxic T lymphocytes and natural killer cells to be triggered. CTL-EXO also contain specific molecules derived from cytotoxic T lymphocytes, such as T cell receptor, CD3 and CD8, and can deliver lethal compounds like perforin, granzymes and lysosomal enzymes to cancer cells. It is noteworthy that, although initial studies with mouse models have shown incredible results, clinical trials in tumor patients have not shown similar success in terms of their anticancer effect. **Conclusion:** The current studies and the growing body of evidence indicate that, despite some obstacles, EXO-based cancer therapy has shown promising results in various experimental settings. Thus, future research in this field is needed to overcome the remaining obstacles and to get even closer to the development of effective cancer vaccines.
Keywords: exosomes; cancer vaccines; immunotherapy.

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MOLECULAR DYNAMICS IN THE STUDY OF THE NEUTRALIZATION POTENTIAL OF IgA, IgM AND IgG ANTIBODIES AGAINST SARS-COV-2 INFECTION

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Background: The emergence of new variants of SARS-CoV-2 virus was the main reason for the drastic increase in the number of cases; for example, the serious second wave of infections in the city of Manaus in early 2021. Thus, we set out to understand which mutations in the spike protein could maximize the immunogenicity elicited by the inactivated antigen. Finally, we elucidated which class of antibodies have the greatest potential for neutralization against the virus. **Methods:** All bioinformatics techniques addressed in this research were possible with the help of the Schrodinger Maestro 2021-2 software. The crystallographic structures were obtained from the Protein Data Bank (PDB). The ACE2-RBD complex (PDB ID: 6M0J) with the original strain from Wuhan was used. Molecular dynamics simulations at 100 ns were performed and the affinity value of the spike protein neutralization potential for IgG (PDB ID: 7BZ5), IgM (PDB ID: 2AGJ) and IgA (PDB ID: 1OW0) antibodies were also quantified. Finally, Monte Carlo simulations using the "Affinity Maturation" functionality were also used to find mutations in the antigen that maximize antibody-antigen affinity. **Results:** From the simulations, it was noticed that the value of the RMSD of structural alignment for the initial and final conformation of the ACE2-RBD complex after 100 ns of simulation was lower for variant P.1, and presented a value of 2.052Å; while, for Omicron, the value was 2.669Å. In other words, this may translate into greater structural stability and, therefore, lower affinity for the ACE2 receptor against P.1. This may explain that the large number of lives lost was not a consequence of a greater virulence of P.1, but possibly due to other factors such as socio-economic issues. Regarding the neutralization of the antigen, the dimeric form of the IgA antibody was superior to all antibodies, which was verified by a more spontaneous value for the predicted Gibbs free energy of -184.27 kcal/mol. We also proposed some mutations in the antigen referring to the IgG antibody B38, among which we had G339Q, T345R, F347C, which resulted in a maximized affinity of -55.479 kcal/mol. **Conclusions:** Despite the results being promising, it would still be essential to confirm all the finding through experimental tests. Furthermore, the simulations indicate that not only molecular issues but at issues at the social level may have played a central role in this pandemic and, for that reason, it was also a syndemic.

Keywords: SARS-CoV-2, variants of concern, neutralizing antibodies, molecular dynamics, affinity maturation.

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DENDRITIC CELLS IN ACUTE CELLULAR IMMUNITY AMONG INFECTED PATIENTS WITH SARS-COV-2: AN IMMUNE REVIEW

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Background: SARS-CoV-2 caused the 2020 pandemic in less than four months, and it is still responsible for many cases around the world. Due to high rate of contamination, the incidence increased over time, together with the death rates. The immune system plays a pivotal role on viral clearance, since it is the main factor involved in recognition, processing, and elimination of pathogens. These events are mediated mainly by dendritic cells (DC), which are the main cells in adaptive immunity, through recognition and viral presentation to T and B lymphocytes. Yet, few studies evaluate the participation of DCs and its subtypes on COVID-19 disease activity, which highlights the need to increase comprehension of DCs on innate and adaptive immunity among those patients infected with SARS-CoV-2. **Methods:** This review was conducted via searches of Pubmed and Scielo for original papers, published between 2019 and 2022, and written in English, using the following descriptors: "COVID-19", "immune response", "dendritic cells", "inflammation" and "adaptive immunity". Sixteen original papers were selected for use in this review. **Results**: In SARS-CoV-2 infection, plasmacytoid dendritic cells induce the production of pro-inflammatory cytokines, such as TNF-α, IL-6 and CXCL8, which leads to the cytokine storm, and which is a key factor in disease severity in infected patients. During the initial phases of infection, plasmacytoid DCs rapidly lose their ability to produce antiviral mediators due to intracellular mechanisms, which causes a low count, but also limits type I IFN, and contributes to viral persistence. The reduction in activation and maturation of DCs interfere in antigen presentation, and culminate in a further low cellular response and worse patient prognosis. Myeloid DCs express low HLA-DR in membranes, but there are few, if any, functional alterations. **Conclusion:** Plasmacytoid DCs play an important role in acute inflammation, and we strongly believe there is a pivotal participation in the cytokine storm and, subsequently, in severity; however, few studies support further conclusions regarding DCs as leaders in inflammatory conditions experienced by severe patients. Instead, we must consider that more studies are needed to improve the knowledge of cellular immunity that is available, and maybe suggest a biomarker for prognosis in future cases.

Keywords: COVID-19; immune response; inflammation; adaptive immunity.

Financial Support: FAPEAM, CAPES and CNPq.