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LINHA DE PESQUISA: COAGULOPATIAS (7 artigos)

1- Haemophilia, 29(2): 668-670, 2023.

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Prevalence of sporadic haemophilia A

Márcio A P Santana[1,2], Daniel G Chaves[1], Ricardo M Camelo[2], Luciana W Zuccherato[3], Letícia L Jardim[4], Suely M Rezende[2]; in behalf of the HEMFIL and BrazIT Study Groups*[1]

1. Fundação Hemominas, Belo Horizonte, Minas Gerais, Brazil; 2. Faculty of Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil; 3. Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil; 4. Instituto René Rachou, Fundação Oswaldo Cruz, Belo Horizonte, Minas Gerais, Brazil.

No abstract available (Letter)

2- Pediatric Hematology and Oncology, 41(1): 74-80, 2024. Epub 2023 Feb 24.

https://doi.org/10.1080/08880018.2023.2182853

Changing recombinant factor VIII to plasma-derived factor VIII during immune tolerance induction

Maíse Moreira Dias[1], Ricardo Mesquita Camelo[1,2], Laura Peixoto de Magalhães[1], Letícia Lemos Jardim[1,2], Andrea Gonçalves de Oliveira[3], Rosângela de Albuquerque Ribeiro[4,5], Vivian Karla Brognoli Franco[6], Fábia Michelle Rodrigues de Araújo Callado[7], Cláudia Santos Lorenzato[8], Suely Meireles Rezende[1]; Brazilian Immune Tolerance (BrazIT) Study group

1. Faculty of Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil; 2. Department of Clinical Epidemiology, Leiden University Medical Centre, Leiden, the Netherlands; 3. Fundação HEMOMINAS, Belo Horizonte, Brazil; 4. Centro de Hematologia e Hemoterapia do Ceará (HEMOCE), Fortaleza, Brazil; 5. Hospital

Universitário Walter Cantídeo, Universidade Federal do Ceará, Fortaleza, Brazil; 6. Centro de Hematologia e Hemoterapia de Santa Catarina (HEMOSC), Florianópolis, Brazil; 7. Fundação de Hematologia e Hemoterapia de Pernambuco (HEMOPE), Recife, Brazil; 8. Hemocentro do Paraná (HEMEPAR), Curitiba, Brazil.

No abstract available (Letter)

3- Viruses, 15(4): 938, 2023.

https://doi.org/10.3390/v15040938

Inflammatory Response and Activation of Coagulation after COVID-19 Infection

Anna Glória Fonseca Teodoro[1], Wellington Francisco Rodrigues[1], Thais Soares Farnesi-de-Assunção[1], Anna V Bernardes E Borges[1], Malu Mateus Santos Obata[1], José Rodrigues do Carmo Neto[1], Djalma A Alves da Silva[1], Leonardo E Andrade-Silva[1], Chamberttan S Desidério[1], Juliana C Costa-Madeira[1], Rafaela M Barbosa[1], Andrezza C C Hortolani Cunha[2], Loren Q Pereira[3], Fernanda Bernadelli de Vito[3], Sarah Cristina Sato Vaz Tanaka[3], Fernanda R Helmo[1], Marcela Rezende Lemes[1], Laís M Barbosa[1], Rafael O Trevisan[1], Fabiano V Mundim[1], Ana Carolina M Oliveira-Scussel[1], Paulo Roberto Resende Junior[1], Ivan B Monteiro[4,5], Yulsef M Ferreira[5], Guilherme H Machado[6], Kennio Ferreira-Paim[1], Hélio Moraes-Souza[3], Carlo José Freire de Oliveira[1], Virmondes Rodrigues Júnior[1], Marcos Vinicius da Silva[1]

1. Department of Immunology, Microbiology and Parasitology, Federal University of Triângulo Mineiro, Uberaba, Brazil; 2. Postgraduate Program in Physiological Sciences, Federal University of Triângulo Mineiro, Uberaba, Brazil; 3. Laboratory of Hematological Research of the Federal University of Triângulo Mineiro and Regional Blood Center of Uberaba-Hemominas Foundation, Uberaba, Brazil; 4. UNIMED São Domingos Hospital, Uberaba, Brazil; 5. José Alencar Gomes da Silva Regional Hospital, Uberaba, Brazil; 6. Mário Palmério University Hospital, Uberaba, Brazil.

SARS-CoV-2 (COVID-19) infection is responsible for causing a disease with a wide spectrum of clinical presentations. Predisposition to thromboembolic disease due to excessive inflammation is also attributed to the disease. The objective of this study was to characterize the clinical and laboratory aspects of hospitalized patients, in addition to studying the pattern of serum cytokines, and associate them with the occurrence of thromboembolic events.

Methodology: A retrospective cohort study with 97 COVID-19 patients hospitalized from April to August 2020 in the Triângulo Mineiro macro-region was carried out. A review of

medical records was conducted to evaluate the clinical and laboratory aspects and the frequency of thrombosis, as well as the measurement of cytokines, in the groups that presented or did not present a thrombotic event.

Results: There were seven confirmed cases of thrombotic occurrence in the cohort. A reduction in the time of prothrombin activity was observed in the group with thrombosis. Further, 27.8% of all patients had thrombocytopenia. In the group that had thrombotic events, the levels of IL1b, IL-10, and IL2 were higher ($p < 0.05$).

Conclusions: In the studied sample, there was an increase in the inflammatory response in patients with thrombotic events, confirmed by the increase in cytokines. Furthermore, in this cohort, a link was observed between the IL-10 percentage and an increased chance of a thrombotic event.

4- Annals of Hematology, 102(7): 1939-1949, 2023.

https://doi.org/10.1007/s00277-023-05262-x

Deficiency of coagulation factors is associated with the bleeding diathesis of severe yellow fever

Mariana Brandão Franco[1], Leticia Lemos Jardim[1], Beatriz Nogueira de Carvalho[2], Fernando Basques[2], Daniel Dias Ribeiro[3], Leonardo Soares Pereira[4], Suely Meireles Rezende[1]

1. Faculty of Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil; 2. Hemocentro de Belo Horizonte, Fundação HEMOMINAS, Belo Horizonte, Minas Gerais, Brazil; 3. Hematology Unit, University Hospital, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil; 4. Hospital Eduardo de Menezes, Fundação Hospitalar do Estado de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil.

Yellow fever (YF) is an acute tropical infectious disease caused by an arbovirus and can manifest as a classic hemorrhagic fever. The mechanism of the bleeding diathesis in YF is not well understood. We assessed clinical and laboratory data (including a panel of coagulation tests) from 46 patients with moderate (M) and severe (S) YF admitted to a local hospital between January 2018 and April 2018. Among 46 patients, 34 had SYF of whom 12 (35%) patients died. A total of 21 (45%) patients developed some type of bleeding manifestation and 15 (32%) presented severe bleeding. Patients with SYF had more severe thrombocytopenia ($p = 0.001$); prolonged activated partial thromboplastin time (aPTT) and thrombin time (TT) ($p = 0.03$ and $p = 0.005$, respectively); reduced plasma levels of coagulation factor (F) II ($p < 0.01$), FIX ($p = 0.01$), and FX ($p = 0.04$); and D-dimer levels almost 10 times higher ($p < 0.01$) when compared with patients with MYF. Patients who died had more bleeding ($p = 0.03$), more major bleeding ($p = 0.03$),

prolonged international normalized ratio (INR) and aPTT (p = 0.003 and p = 0.002, respectively), as well as lower activity of FII (p = 0.02), FV (p = 0.001), FVII (p = 0.005), FIX (p = 0.01), and protein C (p = 0.01) than the ones who survived. FVIII levels were either normal or increased in all patients studied. Our results suggest that the bleeding diathesis of SYF is associated with the deficiency of coagulation factors produced by the liver. Prolonged INR and aPTT and reduced FII, FV, FVII, FIX, and protein C were associated with death.

5- Haemophilia, 29(5): 1366-1368, 2023.

https://doi.org/10.1111/hae.14823

Germline variants of the immune checkpoint proteins PD-1, PD-l1 and CTLA-4 and immune tolerance induction outcome in patients with inherited haemophilia A

Luciana W Zuccherato[1], Ricardo M Camelo[2], Daniel G Chaves[3], Suely M Rezende[2]

1. Department of Biochemistry and Immunology, Institute of Biological Sciences, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil; 2. Department of Internal Medicine, Faculty of Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil; 3. Fundação HEMOMINAS, Belo Horizonte, Brazil.

No abstract available (Letter)

6- Revista Brasileira de Cancerologia, 69(1): e-042995, 2023.

https://doi.org/10.32635/2176-9745.RBC.2023v69n1.2995

Mucocutaneous Hyperpigmentation Associated with Hydroxyurea Therapy in a Patient with Essential Thrombocythemia: Case Report

Daniela de Oliveira Werneck Rodrigues[1,2,3]; Augusto Cézar Apolinário dos Santos[3]; Thais Sette Espósito[3]; Lucas Augusto Niess Soares Fonseca[3]; Lucas Barra Mathiasi[3]; Nathália Chebli de Abreu[4]; Monica de Albuquerque Costa[5]; Nathalia Noyma Sampaio Magalhães[6]; Júlia Campos Fabri[6]

1. Fundação Hemominas, Juiz de Fora (MG), Brasil; 2. Instituto Oncológico de Juiz de Fora; 3. Centro Universitário Presidente Antônio Carlos (Unipac-JF), Juiz de Fora (MG), Brasil; 4. Hospital Eduardo de Menezes, Belo Horizonte (MG), Brasil; 5. Serviço de Dermatologia da Prefeitura Municipal de Juiz de Fora, Juiz de Fora (MG), Brasil; 6. Faculdade de Ciências Médicas e da Saúde de Juiz de Fora (Suprema), Juiz de Fora (MG), Brasil.

Introdução: A hiperpigmentação mucocutânea é uma condição dermatológica que pode estar relacionada a tratamentos quimioterápicos, a exemplo das terapias com uso de hidroxiureia (HU). A HU é um fármaco citostático de amplo uso nas doenças mieloproliferativas e compõe a principal linha de tratamento da trombocitemia essencial (TE). O presente estudo tem por objetivo relatar um caso raro de hiperpigmentação mucocutânea em um paciente com TE. Relato do caso: Paciente do sexo masculino, 68 anos de idade, 89 kg, com diagnóstico de TE, em uso de HU 2 g/dia. Com três meses de terapia, apresentou lesões hiperpigmentadas de coloração acastanhadas em pele das mãos e mucosa oral (língua). Em decisão partilhada com o médico-assistente, o paciente optou pela continuação do uso do medicamento. Após seis anos de acompanhamento, as lesões mantêm-se estáveis. Conclusão: A hiperpigmentação mucocutânea associada à terapia com HU é um evento benigno secundário ao uso do fármaco e não exige a interrupção de uso, porém, sua retirada, ou redução das doses, geralmente leva à diminuição ou ao desaparecimento das lesões.

7- Haemophilia, 30(1): 241-244, 2024. Epub 2023 Oct 23.

https://doi.org/10.1111/hae.14893

Blue toe syndrome, severe haemophilia A and emicizumab

Patrícia Santos Resende Cardoso[1,2], Camila Beatriz Pereira Gomes da Silva[3], Eliabe Silva de Abreu[3], Andrea Gonçalves Oliveira[2], Isabel Figueiredo de Magalhães Pereira[4], Túlio Pinho Navarro[5], Suely Meireles Rezende[6]

1. Hematology and Oncology Unit, University Hospital, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil; 2. Hematology, HEMOMINAS Foundation, Belo Horizonte, Minas Gerais, Brazil; 3. Haemostasis and Thrombosis Study Group, Faculty of Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil; 4. Vascular Surgery, University Hospital, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil; 5. Department of Surgery, Faculty of Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil; 6. Department of Internal Medicine, Faculty of Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil.

No abstract available (Letter)

LINHA DE PESQUISA: HEMOGLOBINOPATIAS (8 artigos)

1- British Journal of Haematology, 201(2): 343-352, 2023.

https://doi.org/10.1111/bjh.18637

Genome-wide association study of early ischaemic stroke risk in Brazilian individuals with sickle cell disease implicates ADAMTS2 and CDK18 and uncovers novel loci

Eric Jay Earley[1], Shannon Kelly[2,3], Fang Fang[1], Cecília Salete Alencar[4], Daniela de Oliveira Werneck Rodrigues[5], Dahra Teles Soares Cruz[6], Jonathan M Flanagan[7], Russell E Ware[8], Xu Zhang[9], Victor Gordeuk[9], Mark Gladwin[10], Yingze Zhang[10], Mehdi Nouraie[10], Sergei Nekhai[11], Ester Sabino[12], Brian Custer[3,13], Carla Dinardo[12], Grier P Page[1]; International Component of the NHLBI Recipient Epidemiology and Donor Evaluation Study (REDS-III) and the NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium

1. RTI International, Research Triangle Park, North Carolina, Durham, USA; 2. Benioff Children's Hospital, University of San Francisco, San Francisco, California, USA; 3. Vitalant Research Institute, San Francisco, California, USA; 4. Laboratório de Medicina Laboratorial LIM 03- HCFMUSP, São Paulo, Brazil; 5. Fundação Hemominas Juiz de Fora, Juiz de Fora, Brazil; 6. Department of Hematology, Fundação de Hematologia e Hemoterapia de Pernambuco, HEMOPE, Pernambuco, Brazil; 7. Division of Hematology and Oncology, Department of Pediatrics, Baylor College of Medicine, Houston, Texas, USA; 8. Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA; 9. Department of Medicine, University of Illinois at Chicago, Chicago, Illinois, USA; 10. Division of Pulmonary, Allergy and Critical Care Medicine, Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA; 11. Department of Medicine, Center for Sickle Cell Disease, Howard University, Washington, District of Columbia, USA; 12. Instituto de Medicina Tropical, University of São Paulo, São Paulo, Brazil; 13. Department of Laboratory Medicine, University of California, San Francisco, USA.

Ischaemic stroke is a common complication of sickle cell disease (SCD) and without intervention can affect 11% of children with SCD before the age of 20. Within the Trans-Omics for Precision Medicine (TOPMed), a genome-wide association study (GWAS) of ischaemic stroke was performed on 1333 individuals with SCD from Brazil (178 cases, 1155 controls). Via a novel Cox proportional-hazards analysis, we searched for variants associated with ischaemic stroke occurring at younger ages. Variants at genome-wide significance ($p < 5 \times 10^{-8}$) include two near genes previously linked to non-SCD early-onset stroke (<65 years): ADAMTS2 (rs147625068, $p = 3.70 \times 10^{-9}$) and CDK18 (rs12144136, $p = 2.38 \times 10^{-9}$). Meta-analysis, which included the independent SCD cohorts Walk-PHaSST and PUSH, exhibited consistent association for variants rs1209987 near gene TBC1D32 ($p = 3.36 \times 10^{-10}$), rs188599171 near CUX1 ($p = 5.89 \times 10^{-11}$), rs77900855 near BTG1 ($p = 4.66 \times 10^{-8}$), and rs141674494 near VPS13C (1.68×10^{-9}).

Findings from this study support a multivariant model of early ischaemic stroke risk and possibly a shared genetic architecture between SCD individuals and non-SCD individuals younger than 65 years.

2- Advances in Skin & Wound Care, 36(2): 98-105, 2023.

https://doi.org/10.1097/01.ASW.0000911152.41719.e5

Factors Associated with Leg Ulcers in Adults with Sickle Cell Disease in Brazil

Valquíria Reis de Souza[1], Shannon Kelly[2], Ester Cerdeira Sabino[1], Franciane Mendes de Oliveira[1], Tassila Silva[3], Carolina Miranda Teixeira[4], Claudia Máximo[5], Paula Loureiro[6], Anna Barbara de Freitas Carneiro-Proietti[7], Isabel Gomes[8], Brian Custer[2,9], Cesar de Almeida-Neto[10,11]

1. Instituto de Medicina Tropical, University of São Paulo, Brazil; 2. Vitalant Research Institute, San Francisco, California; 3. Faculdade de Ciências Médicas de Minas Gerais, Belo Horizonte; 4. Faculdade de Medicina, Universidade Federal de Minas Gerais; 5. Hemorio, Hemocentro do Rio de Janeiro; 6. Hemope and Universidade de Pernambuco, Recife; 7. Fundação Hemominas, Hemocentro de Minas Gerais; 8. Universidade Federal de Minas Gerais; 9. Laboratory Medicine, University of California, San Francisco; 10. Faculdade de Medicina da Universidade de São Paulo; 11. Fundação Pró-Sangue Hemocentro de São Paulo.

Objective: To define the prevalence of leg ulcers and identify the clinical and laboratory factors associated with leg ulcers in adult participants.

Methods: The authors conducted a cross-sectional study of 1,109 patients who were 18 years or older with SS or Sβ0-thalassemia genotypes from a Brazilian cohort. Investigators assessed the prevalence of factors associated with leg ulcers from 2013 to 2017.

Results: The prevalence of leg ulcers was 21%. Increasing age (odds ratio [OR], 1.07; range, 1.06-1.09), male sex (OR, 2.03; range, 1.44-2.87), treatment with chronic transfusion therapy (OR, 1.88; range, 1.15-3.03), higher indirect bilirubin levels (OR, 1.48; range, 1.02-2.16), and low hemoglobin levels (OR, 2.17; range, 1.52-3.11) were associated with leg ulcers. Participants who self-reported as Black (OR, 6.75; range, 2.63-21.32), mixed (OR, 3.91; range, 1.55-12.20), and other/unknown (OR, 3.84; range, 1.04-15.24) were more likely to have leg ulcers compared with those who self-reported as White.

Conclusions: The prevalence of leg ulcers in this Brazilian cohort was higher than the prevalence reported in developed countries. Known factors such as age and male sex were corroborated. The increased bilirubin level and decreased hemoglobin levels among participants with leg ulcers support the hypothesis that hemolysis is correlated

with leg ulcer pathogenesis. Self-reported black skin color was an independent predictor of leg ulcers and warrants further study to understand the etiology and implications of this finding.

3- Annals of Hematology, 102(5): 1019-1027, 2023.

https://doi.org/10.1007/s00277-023-05150-4

Estimated glomerular filtration rate in Brazilian adults with sickle cell disease: results from the REDS-III multicenter cohort study

André Rolim Belisário[1,2], Ana Cristina Simões E Silva[3], Isabel Cristina Gomes Moura[4], Anna Bárbara Carneiro-Proietti[5], Ester Cerdeira Sabino[6], Paula Loureiro[7,8], Cláudia Máximo[9], Miriam V Flor-Park[10], Daniela de Oliveira Werneck Rodrigues[5], Mina Cintho Ozahata[11], Rosimere Afonso Mota[5], Carla Luana Dinardo[12], Shannon Kelly[13], Brian Custer[14,15]; Recipient Epidemiology and Donor Evaluation Study (REDS-III) International Component Brazil

1. Centro de Tecidos Biológicos de Minas Gerais, Fundação Hemominas; 2. Laboratório Interdisciplinar de Investigação Médica, Faculdade de Medicina, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, Brazil; 3. Laboratório Interdisciplinar de Investigação Médica, Faculdade de Medicina, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, Brazil; 4. Faculdade Ciências Médicas, Belo Horizonte, MG, Brazil; 5. Centro de Tecidos Biológicos de Minas Gerais, Fundação Hemominas; 6. Faculdade de Medicina (FMUSP) and Instituto de Medicina Tropical, Universidade de São Paulo, São Paulo, Brazil; 7. Fundação Hemope, Recife, PE, Brazil; 8. Universidade de Pernambuco, Recife, PE, Brazil; 9. Hemorio, Rio de Janeiro, Brazil; 10. ITACI, Unidade de Onco-Hematologia, Instituto da Criança, HCFMUSP, São Paulo, Brazil; 11. Department of Computer Science - DCC, University of São Paulo, São Paulo, Brazil; 12. Pró-Sangue, São Paulo, Brazil; 13. UCSF Benioff Children's Hospital, Oakland, CA, USA; 14. Vitalant Research Institute, San Francisco, CA, USA; 15. Department of Laboratory Medicine, UCSF, San Francisco, CA, USA.

Chronic kidney disease (CKD) has a significant impact on sickle cell disease (SCD) morbidity and mortality. Early identification of individuals at highest risk of developing CKD may allow therapeutic intervention to prevent worse outcomes. This study aimed to evaluate the prevalence and risk factors for reduced estimated glomerular filtration rate (eGFR) among adults with SCD in Brazil. Participants in the REDS-III multicenter SCD cohort with more severe genotypes aged ≥ 18 years with at least two serum creatinine values were analyzed. The eGFR was calculated using the Jamaica Sickle Cell Cohort Study GFR equation. The eGFR categories were defined according to the K/DOQI. Participants with eGFR ≥ 90 were compared to those with those with eGFR < 90. Among

the 870 participants, 647 (74.4%) had eGFR ≥ 90, 211 (24.3%) had eGFR 60 to 89, six (0.7%) had eGFR 30 to 59, and six (0.7%) had ESRD. Male sex (OR: 37.3; 95%CI: 22.4-65.1), higher age (OR: 1.04; 95%CI: 1.02-1.06), higher diastolic blood pressure (OR: 1.03; 95%CI: 1.009-1.06), lower Hb (OR: 0.80; 95%CI: 0.68-0.93), and lower reticulocytes (OR: 0.94; 95%CI: 0.89-0.99) levels were independently associated with eGFR < 90. There was a trend towards higher odds of death in participants with eGFR < 90 (OR: 1.8; 95%CI: 0.95-3.32; p = 0.065). In turn, participants with eGFR < 60 had a 12.2 (95%CI: 2.1-96.9) times higher odds for death when compared to those with eGFR ≥ 60. In this study, eGFR < 90 was observed in one-quarter of adults. Older age, male sex, higher diastolic blood pressure, lower hemoglobin, and lower reticulocyte levels were associated with occurrence of eGFR < 90. Estimated GFR < 60 increased the risk of mortality.

4- Blood Cells, Molecules & Diseases, 104: 102795, 2024. Epub 2023 Aug 30.

https://doi.org/10.1016/j.bcmd.2023.102795

Severe clinical picture in a cohort of six Brazilian children with hemoglobin Sβ-thalassemia IVS-I-5 G>A

Marcos Borato Viana[1], Érica Louback Oliveira[1], André Rolim Belisário[2]

1. Faculdade de Medicina, Núcleo de Ações e Pesquisa em Apoio Diagnóstico (NUPAD), Universidade Federal de Minas Gerais, Belo Horizonte, Brazil; 2. Centro de Tecidos Biológicos de Minas Gerais, Fundação Hemominas, Lagoa Santa, Minas Gerais, Brazil.

No abstract available (Letter)

5- Hematology, Transfusion and Cell Therapy, 45 (Suppl 2): S113-S118, 2023.

https://doi.org/10.1016/j.htct.2022.09.1184

Analysis of the costs of the basic care line for sickle cell disease in Brazilian children under 5 years of age

Franciane Vilela Réche Réche da Motta[1], Samara De Paula Silva Souza[2], Lucas Augusto Niess Soares Fonseca[3], Alfredo Chaoubah[1], Daniela de Oliveira Werneck Rodrigues[4]

1. Universidade Federal de Juiz de Fora, MG, Brazil; 2. Faculdade de Ciências Médicas e da Saúde de Juiz de Fora, Juiz de Fora, MG, Brazil; 3. Universidade Presidente Antônio Carlos Juiz de Fora, Brazil; 4. Fundacao Hemominas, Juiz de Fora, MG, Brazil.

Objective: To evaluate and estimate the cost of basic care in sickle cell disease (SCD) for patients under five years of age, within the scope of the Unified Health System (SUS) and to discuss the costs related to possible complications of the disease from the literature.

Methods: The main management and conduct recommendations in the SCD up to five years of age, with healthy and baseline health status, were extracted from the Basic Guidelines of the Care Line in the SCD of the Ministry of Health. Systematic data regarding costs of medicines were extracted from the Medicine Market Regulation Chamber. The SUS Table of Procedures, Medicines and Orthotics, Prosthetics and Auxiliary Means of Movement Management System was the guide for the values of complementary exams, as well as for medical consultations. The values applied to calculate the vaccination schedule were extracted from the Pan American Health Organization, adopting the perspective of the SUS-paying costs.

Results: The total cost obtained for basic care of SCD in children up to five years of age, including the use of antibiotic prophylaxis, immunizations and the performance of transcranial Doppler ultrasound in the prevention and early detection of cerebrovascular accidents was, on average, $1020.96.

Conclusion: The cost-effectiveness of prophylaxis in SCD, up to five years of age, exceeds the expenses resulting from hospitalizations due to complications of the disease. The study of expenses associated with SCD could be used to establish public policies, improve prevention strategies and treat the symptoms and complications of the disease.

6- Revista da Associação Médica Brasileira (1992), 69(10): e20210819, 2023.

https://doi.org/10.1590/1806-9282.20210819

Peak nasal inspiratory flow in children and adolescents with sickle cell disease: a case-control study

Ana Karine Vieira[1], Cristina Gonçalves Alvim[2], Clara Polito Braga[2], Ricardo Reis Dinardi[3], Marcos Vinícius Domingues Borba[2], Ricardo Manoel Oliveira Rodrigues[2], Cássio da Cunha Ibiapina[2]

1. Hemominas Foundation, Belo Horizonte (MG), Brazil; 2. University Hospital, Universidade Federal de Minas Gerais, Pediatric Pulmonology Unit - Belo Horizonte (MG), Brazil; 3. Pontifícia Universidade Católica de Minas Gerais - Belo Horizonte (MG), Brazil.

Objective: Sickle cell disease is the most frequent of the hereditary hemoglobinopathies and it presents multisystemic effects. A manifestation that is commonly found in sickle cell disease is upper airway obstruction, particularly adenotonsillar hypertrophy. This

study aims to evaluate the peak nasal inspiratory flow measurements of children and adolescents with sickle cell disease.

Methods: This is a case-control study on children aged between 8 and 15 years who were diagnosed with sickle cell disease. Peak nasal inspiratory flow measurements were obtained from patients.

Results: A total of 279 patients were enrolled in this study, with 93 in the case group and 186 in the control group. The case group had an 82.83% chance of having lower peak nasal inspiratory flow values than the control group. In the case group, 75% of the peak nasal inspiratory flow values were in the lower standards, whereas in the control group, only 25% were in the lower standards.

Conclusion: This study showed a high prevalence of reduced peak nasal inspiratory flow values in children with sickle cell disease and could certainly be incorporated into the day-to-day clinical evaluation of patients as a screening instrument.

7- Blood Advances, 8(2): 365-368, 2024. Epub 2023 Dec 6.

https://doi.org/10.1182/bloodadvances.2023011765

Natural history of albuminuria in a large cohort of children and adolescents with sickle cell anemia from Brazil

André Rolim Belisário[1], Jéssica Alves Almeida[2], Ana Cristina Simões e Silva[2]

1. Fundação Hemominas, Belo Horizonte, Brazil; 2. Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil.

No abstract available (Commentary)

8- Hematology, Transfusion and Cell Therapy, S2531-1379(23)02598-1, 2023.

https://doi.org/10.1016/j.htct.2023.11.002

Clinical, laboratory, and molecular characteristics of a cohort of children with hemoglobinopathy S/beta-thalassemia

Érica Louback Oliveira[1], André Rolim Belisário[2], Natiely Pereira Silva[1], Paulo Val Rezende[3], Maristela Braga Muniz[3], Larissa Maira Moura Oliveira[1], Cibele Velloso-Rodrigues[4], Marcos Borato Viana[5]

1. Faculdade de Medicina/Núcleo de Ações e Pesquisa em Apoio Diagnóstico (NUPAD), UFMG, Belo Horizonte, MG, Brazil; 2. Centro de Tecidos Biológicos de Minas Gerais, Fundação Hemominas, Lagoa Santa, MG, Brazil; 3. Ambulatório do Hemocentro de Belo Horizonte, Fundação Hemominas, Belo Horizonte, MG, Brazil; 4. Departamento de Ciências Básicas da Vida, Instituto de Ciências da Vida, Universidade Federal de Juiz de Fora, Governador Valadares, MG, Brazil; 5. Faculdade de Medicina/Núcleo de Ações e Pesquisa em Apoio Diagnóstico (NUPAD), UFMG, Belo Horizonte, MG, Brazil.

Introduction: Hemoglobinopathy Sβ-thalassemia (HbSβ-thal) has a wide range of clinical and laboratory severity. There is limited information on the natural history of HbSβ-thal and its modulating factors. We described the molecular, hematological, and clinical characteristics of a cohort of children with HbSβ-thal and estimated its incidence in Minas Gerais, Brazil.

Methods: Laboratory and clinical data were retrieved from medical records. Molecular analysis was performed by HBB gene sequencing, PCR-RFLP, gap-PCR, and MLPA.

Results: Eighty-nine children were included in the study. Fourteen alleles of β-thal mutations were identified. The incidence of HbSβ-thal in the state was 1 per 22,250 newborns. The most common βS-haplotypes were CAR and Benin. The most frequent βthal-haplotypes were V, II, and I. Coexistence of 3.7 kb HBA1/HBA2 deletion was present in 21.3 % of children. β-thalassemia mutations were associated with several clinical and laboratory features. In general, the incidence of clinical events per 100 patient-years was similar for children with HbSβ0-thal, IVS-I-5 G>A, and IVS-I-110 G>A. Children with HbSβ+-intermediate phenotypes had a more severe laboratory and clinical profile when compared with those with HbSβ+-mild ones. βS-haplotypes and α-thalassemia did not meaningfully influence the phenotype of children with HbSβ-thal.

Conclusion: The early identification of β-thalassemia alleles may help the clinical management of these children.

LINHA DE PESQUISA: TRANSPLANTES, ENXERTOS E TERAPIA CELULAR (1 artigo)

1- Transfusion, 63(1): 269-271, 2023.

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Critical failure of a cell therapy products storage tank: Description, investigation and implemented improvements

André Rolim Belisário[1], Elimiramá V C Benfica[1], Luciana de Almeida de Costa[1], Maurício Colombini Martins[1], Roberta Kelly de Andradre[1], Paula Renata Machado Passos Pederzoli[1], Karen de Lima de Prata[1]

1. Centro de Tecidos Biológicos de Minas Gerais-Fundação Hemominas, Lagoa Santa, Minas Gerais, Brazil.

No abstract available (Letter)

LINHA DE PESQUISA: DOENÇAS TRANSMISSÍVEIS POR TRANSFUSÃO E TRANSPLANTE (2 artigos)

1- Transfusion, 63(5): 1044-1049, 2023.

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Leukoreduction as a control measure in transfusion transmission of visceral leishmaniasis

Loren Queli Pereira[1], Sarah Cristina Sato Vaz Tanaka[1], Márcia Maria Ferreira-Silva[1], Francisca Vânia Barreto Aguiar Ferreira Gomes[2], Melissa Palis Santana[3], Paulo Roberto Aguiar[4], Gilberto de Araújo Pereira[5], César Gómez-Hernández[6], Virmondes Rodrigues Junior[6], Fernanda Bernadelli De Vito[1], Helio Moraes-Souza[1]

1. Laboratory of Hematological Research, Triângulo Mineiro Federal University, Uberaba, Brazil; 2. Department of Health of Government of the State of Ceará, Hemoce - Center for Hematology and Hemotherapy of the State of Ceará, Fortaleza, Brazil; 3. Government of Piauí, Hemopi - Hematology and Hemotherapy Center of the State of Piauí, Teresina, Brazil; 4. Hemominas Foundation, Regional Blood Center of Montes Claros (Minas Gerais), Montes Claros, Brazil; 5. Department of Nursing in Education and Community Health, Federal University of Triângulo Mineiro, Uberaba, Brazil; 6. Laboratory of Immunology, Triângulo Mineiro Federal University, Uberaba, Brazil.

Background: Asymptomatic visceral leishmaniasis (VL) infection is a risk for transfusion safety. Leukoreduction has been an alternative for the prevention of some blood-borne diseases, including VL. This study aimed to evaluate the role of leukoreduction of cellular blood components as a control measure for transfusional VL transmission.

Research design and methods: A total of 161 polytransfused patients with non-leukoreduced blood components (HNL), 95 polytransfused with leukoreduced blood components (LH), and 202 non-transfused (NT) from endemic regions for VL and with a similar epidemiological profile. The detection of antibodies against VL was performed by ELISA and the presence of the parasite was investigated by real-time PCR. Statistical significance was defined as $p < .05$.

Results: When comparing three groups, ELISA results were statistically significant (p = .0065). The residual analysis of ELISA showed statistically significant for the HNL group compared to the general group (p = .002; OR: 5.6; CI: 1.7-25.8), demonstrating that individuals who received non-leukoreduced transfusions are five times more likely to acquire *Leishmania infantum* infection than the general.

Discussion: Higher prevalence in the group with HNL and low prevalence in those who received LH, similar to NT patients, highlight the risk of transfusional VL transmission and reinforce the role of leukoreduction in its prevention.

2- Virology Journal, 20(1): 304, 2023.

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Preclinical assessment of an anti-HTLV-1 heterologous DNA/MVA vaccine protocol expressing a multiepitope HBZ protein

DSO Daian E Silva[1,2], LJ Cox[1,2], AS Rocha[1,2], Á Lopes-Ribeiro[1], JPC Souza[3], GM Franco[1,2], JLC Prado[1], TA Pereira-Santos[1,2], ML Martins[2,4], JGA Coelho-Dos-Reis[1,2], TM Gomes-de-Pinho[3], FG Da Fonseca[1,3], EF Barbosa-Stancioli[2,5]

1. Laboratório de Virologia Básica e Aplicada, Departamento de Microbiologia, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais, Av. Antônio Carlos, 6627, Campus Pampulha, Belo Horizonte, MG, CEP 31270-901, Brazil; 2. GIPH - Grupo Interdisciplinar de Pesquisas em HTLV, Interdisciplinary HTLV Research Group, Belo Horizonte, Brazil; 3. Centro de Tecnologia de Vacinas, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, 31270-901, Brazil; 4. Gerência de Desenvolvimento Técnico Científico, Fundação Centro de Hematologia e Hemoterapia do Estado de Minas Gerais - Hemominas, Belo Horizonte, Brazil; 5. Laboratório de Virologia Básica e Aplicada, Departamento de Microbiologia, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais.

Background: Human T-lymphotropic virus 1 (HTLV-1) is associated with the development of several pathologies and chronic infection in humans. The inefficiency of the available treatments and the challenge in developing a protective vaccine highlight the need to produce effective immunotherapeutic tools. The HTLV-1 basic leucine zipper (bZIP) factor (HBZ) plays an important role in the HTLV-1 persistence, conferring a survival advantage to infected cells by reducing the HTLV-1 proteins expression, allowing infected cells to evade immune surveillance, and enhancing cell proliferation leading to increased proviral load.

Methods: We have generated a recombinant Modified Virus Vaccinia Ankara (MVA-HBZ) and a plasmid DNA (pcDNA3.1(+)-HBZ) expressing a multiepitope protein based on peptides of HBZ to study the immunogenic potential of this viral-derived protein in

BALB/c mice model. Mice were immunized in a prime-boost heterologous protocol and their splenocytes (T CD4+ and T CD8+) were immunophenotyped by flow cytometry and the humoral response was evaluated by ELISA using HBZ protein produced in prokaryotic vector as antigen.

Results: T CD4+ and T CD8+ lymphocytes cells stimulated by HBZ-peptides (HBZ42-50 and HBZ157-176) showed polyfunctional double positive responses for TNF-α/IFN-γ, and TNF-α/IL-2. Moreover, T CD8+ cells presented a tendency in the activation of effector memory cells producing granzyme B (CD44+High/CD62L-Low), and the activation of Cytotoxic T Lymphocytes (CTLs) and cytotoxic responses in immunized mice were inferred through the production of granzyme B by effector memory T cells and the expression of CD107a by CD8+ T cells. The overall data is consistent with a directive and effector recall response, which may be able to operate actively in the elimination of HTLV-1-infected cells and, consequently, in the reduction of the proviral load. Sera from immunized mice, differently from those of control animals, showed IgG-anti-HBZ production by ELISA.

Conclusions: Our results highlight the potential of the HBZ multiepitope protein expressed from plasmid DNA and a poxviral vector as candidates for therapeutic vaccine.

LINHA DE PESQUISA: DOAÇÃO DE SANGUE E COMPONENTES (1 artigo)

1- Ciência & Saúde Coletiva, 28(5): 1387-1397, 2023.

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Management of hemotherapy services in the context of the COVID-19 pandemic

Mariluce Karla Bomfim de Souza[1], Patrícia Sodré Araújo[2], Laíse Caroline Costa Soares[2], Júnia Guimarães Mourão Cioffi[3]

1. Instituto de Saúde Coletiva, Universidade Federal da Bahia; 2. Departamento de Ciências da Vida, Universidade do Estado da Bahia. Salvador, BA, Brasil; 3. Fundação Centro de Hematologia e Hemoterapia do Estado de Minas Gerais - Hemominas. Belo Horizonte, MG, Brasil.

This study aimed to analyze the management of hemotherapy services (HS) in the context of the COVID-19 pandemic from the perspective of municipal managers in different regions of Brazil. A qualitative approach with semi-structured interviews was applied to HS managers in the three Brazilian capitals, from different regions of Brazil, during the period between September 2021 and April 2022. The textual content of the interviews was submitted to lexicographic textual analysis using the free access

software, Iramuteq. The managers' perceptions resulted from the descending hierarchical classification (DHC) analysis, which generated six classes: availability of resources for the development of work; installed capacity of services; strategies and challenges for attracting blood donors; risks and worker protection; measures for crisis management; and communication strategies for the adhesion of candidates for donation. The analysis highlighted several strategies used by the management, as well as pointed out limits and challenges for HS organization and management, exacerbated in the context of the pandemic.

LINHA DE PESQUISA: IMUNOHEMATOLOGIA (1 artigo)

1- Transfusion Medicine Reviews, 38(1): 150776, 2023.

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Next Generation Sequencing of Red Blood Cell Antigens in Transfusion Medicine: Systematic Review and Meta-Analysis

Carolina Guimarães Ramos Matosinho, Caroline Graciane Rodrigues Silva, Marina Lobato Martins, Maria Clara Fernandes Silva-Malta

Fundação Hemominas, Belo Horizonte, Minas Gerais, Brazil.

Molecular analysis of blood groups is important in transfusion medicine, allowing the prediction of red blood cell (RBC) antigens. Many blood banks use single nucleotide variant (SNV) based methods for blood group analysis. While this is a well-established approach, it is limited to the polymorphisms included in genotyping panels. Thus, variants that alter antigenic expression may be ignored, resulting in incorrect prediction of phenotypes. The popularization of next-generation sequencing (NGS) has led to its application in transfusion medicine, including for RBC antigens determination. The present review/meta-analysis aimed to evaluate the applicability of the NGS for the prediction of RBC antigens. A systematic review was conducted following a comprehensive literature search in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines. Studies were selected based on predefined criteria and evaluated using Strengthening the Reporting of Observational studies in Epidemiology guidelines. The characteristics and results of the studies were extracted and meta-analysis was performed to verify the agreement between results from standard molecular methods and NGS. Kell (rs8176058), Duffy (rs2814778, rs12078), or Kidd (rs1085396) alleles were selected as a model for comparisons. Additionally, results are presented for other blood group systems. Of the 864 eligible studies identified, 10 met the inclusion criteria and were selected for meta-analysis. The pooled concordance proportion for NGS compared to other methods ranged from 0.982

to 0.994. The sequencing depth coverage was identified as crucial parameters for the reliability of the results. Some studies reported difficulty in analyzing more complex systems, such as Rh and MNS, requiring the adoption of specific strategies. NGS is a technology capable of predicting blood group phenotypes and has many strengths such as the possibility of simultaneously analyzing hundred individuals and gene regions, and the ability to provide comprehensive genetic analysis, which is useful in the description of new alleles and a better understanding of the genetic basis of blood groups. The implementation of NGS in the routine of blood banks depends on several factors such as cost reduction, the availability of widely validated panels, the establishment of clear quality parameters and access to bioinformatics analysis tools that are easy to access and operate.