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Haematology

Evidence Update

January/February 2018

(Bimonthly)

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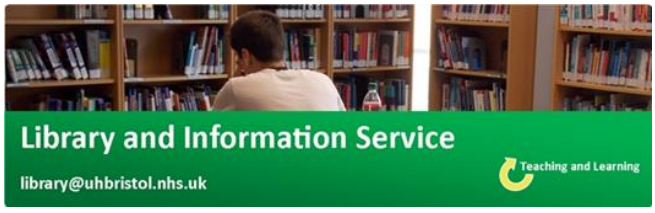

Lunchtime Drop-in Sessions

All sessions last one hour

February (12.00-13.00)

1st (Thu)	**Literature Searching**
9th (Fri)	**Critical Appraisal**
12th (Mon)	**Statistics**
20th (Tue)	**Literature Searching**
28th (Wed)	**Critical Appraisal**

March (13.00-14.00)

8th (Thu)	**Statistics**
12th (Mon)	**Literature Searching**
20th (Tue)	**Critical Appraisal**
28th (wed)	**Statistics**

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Outreach: Your Outreach Librarian can help facilitate evidence-based practice for all in the team, as well as assisting with academic study and research. We also offer one-to-one or small group training in **literature searching, critical appraisal and medical statistics**. Get in touch: library@uhbristol.nhs.uk

Literature searching: We provide a literature searching service for any library member. For those embarking on their own research it is advisable to book some time with one of the librarians for a one-to-one session where we can guide you through the process of creating a well-focused literature research. Please email requests to library@uhbristol.nhs.uk

Contents

Current Journals: Tables of Contents

Click on journal title (+ Ctrl) for hyperlink. If you require full articles please email: library@uhbristol.nhs.uk

Journal	Month	Volume	Issue
Blood	Jan 25, 2018	131	4
Bone Marrow Transplantation	Jan 2018	53	1
British Journal of Haematology	Jan 2018	180	1
Experimental Haematology	Jan 2018	57	-
Haematologica	Jan 2018	103	2
Journal of Clinical Oncology	Feb 2018	36	4
Journal of Thrombosis and Haemostatis	Jan 2018	16	1
Leukaemia Research	Feb 2018	65	-
New England Journal of Medicine	Feb 1, 2018	378	5

Latest Evidence

NICE National Institute for Health and Care Excellence

Blood and immune system conditions

Everything NICE has said on blood and immune system conditions in an interactive flowchart

NICE Pathway Published November 2014 Last updated July 2017

Sickle cell disease: acute painful episode

Everything NICE has said on managing acute painful sickle cell disease episodes in patients presenting to hospital until...

NICE Pathway Published June 2012 Last updated June 2017

Sickle cell and thalassaemia: screening handbook

Source: Public Health England - Source: GOV UK - 09 January 2018

Guidance for healthcare professionals covering the pathway for sickle cell and thalassaemia screening.

Sickle cell and thalassaemia screening: handbook for laboratories

Source: Public Health England - Source: GOV UK - 05 December 2017

documents set out policy and standards for laboratories working with the sickle cell and thalassaemia (SCT) screening...

Sickle cell and thalassaemia screening: outcome data collection template

Source: Public Health England - Source: GOV UK - 08 August 2017

Template to record and submit newborn outcomes data for the sickle cell and thalassaemia (SCT) screening programme.

Sickle cell disease

Source: Clinical Knowledge Summaries - 04 January 2017

Sickle cell disease encompasses a group of inherited conditions which have the inheritance of...

Cochrane Library

Splenectomy versus conservative management for acute sequestration crises in people with sickle cell disease
Shirley Owusu-Ofori and Tracey Remmington
Online Publication Date: November 2017

Prophylactic antibiotics for preventing pneumococcal infection in children with sickle cell disease
Angela E Rankine-Mullings and Shirley Owusu-Ofori
Online Publication Date: October 2017

Treatments for priapism in boys and men with **sickle cell** disease
Francis I Chinegwundoh , Sherie Smith and Kofi A Anie
Online Publication Date: September 2017

Transcutaneous electrical nerve stimulation (TENS) for pain management in **sickle cell** disease
Sudipta Pal , Ruchita Dixit , Soe Moe , Myron A Godinho , Adinegara BL Abas , Samir K Ballas , Shanker Ram and Uduman Ali M Yousuf
Online Publication Date: August 2017

Interventions for treating intrahepatic cholestasis in people with **sickle cell** disease
Arturo J Martí-Carvajal and Cristina Elena Martí-Amarista
Online Publication Date: July 2017

Fluid replacement therapy for acute episodes of pain in people with **sickle cell** disease
Uduak Okomo and Martin M Meremikwu
Online Publication Date: July 2017

Interventions for chronic kidney disease in people with **sickle cell** disease
Noemi BA Roy , Patricia M Fortin , Katherine R Bull , Carolyn Doree , Marialena Trivella , Sally Hopewell and Lise J Estcourt
Online Publication Date: July 2017

Interventions for preventing silent cerebral infarcts in people with **sickle cell** disease
Lise J Estcourt , Patricia M Fortin , Sally Hopewell , Marialena Trivella , Carolyn Doree and Miguel R Abboud
Online Publication Date: May 2017

Hydroxyurea (hydroxycarbamide) for **sickle cell** disease
Sarah J Nevitt , Ashley P Jones and Jo Howard
Online Publication Date: April 2017

Magnesium for treating **sickle cell** disease
Nan Nitra Than , Htoo Htoo Kyaw Soe , Senthil K Palaniappan , Adinegara BL Abas and Lucia De Franceschi
Online Publication Date: April 2017

Vitamin D supplementation for **sickle cell** disease
Htoo Htoo Kyaw Soe , Adinegara BL Abas , Nan Nitra Than , Han Ni , Jaspal Singh , Abdul Razzak Bin Mohd Said and Ifeyinwa Osunkwo
Online Publication Date: January 2017

Blood transfusion for preventing primary and secondary stroke in people with **sickle cell** disease
Lise J Estcourt , Patricia M Fortin , Sally Hopewell , Marialena Trivella and Winfred C Wang
Online Publication Date: January 2017

Growth hormone therapy for people with thalassaemia
Chin Fang Ngim , Nai Ming Lai , Janet YH Hong , Shir Ley Tan , Amutha Ramadas , Premala Muthukumarasamy and Meow-Keong Thong
Online Publication Date: September 2017

Prophylactic **platelet** transfusions prior to surgery for people with a low **platelet** count [protocol]
Lise J Estcourt , Reem Malouf , Carolyn Doree , Marialena Trivella , Sally Hopewell and Janet Birchall
Online Publication Date: September 2017

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What's new in hematology

Authors: Rebecca F Connor, MD; Jennifer S Tirnauer, MD; Alan G Rosmarin, MD

Literature review current through: Dec 2017. | **This topic last updated:** Jan 30, 2018.

Overview of the management and prognosis of sickle cell disease

Authors: Joshua J Field, MD; Elliott P Vichinsky, MD; Michael R DeBaun, MD, MPH

Literature review current through: Dec 2017. | **This topic last updated:** Oct 23, 2017.

Overview of the clinical manifestations of sickle cell disease

Author: Elliott P Vichinsky, MD

Literature review current through: Dec 2017. | **This topic last updated:** Nov 08, 2017.

Overview of variant sickle cell syndromes

Author: Elliott P Vichinsky, MD

Literature review current through: Dec 2017. | **This topic last updated:** Jan 09, 2018.

Diagnosis of sickle cell disorders

Authors: Elliott P Vichinsky, MD; Donald H Mahoney, Jr, MD

Literature review current through: Dec 2017. | **This topic last updated:** Jan 09, 2018.

Red blood cell transfusion in sickle cell disease

Authors: Michael R DeBaun, MD, MPH; Elliott P Vichinsky, MD

Literature review current through: Dec 2017. | **This topic last updated:** Dec 19, 2017.

Overview of the pulmonary complications of sickle cell disease

Authors: Elizabeth S Klings, MD; Harrison W Farber, MD

Literature review current through: Dec 2017. | **This topic last updated:** Nov 28, 2017.

Hydroxyurea use in sickle cell disease

Authors: Griffin P Rodgers, MD; Alex George, MD, PhD

Literature review current through: Dec 2017. | **This topic last updated:** Dec 04, 2017.

Pregnancy in women with sickle cell disease

Author: Elliott P Vichinsky, MD

Literature review current through: Dec 2017. | **This topic last updated:** Jul 27, 2017.

Vaso-occlusive pain management in sickle cell disease

Authors: Michael R DeBaun, MD, MPH; Elliott P Vichinsky, MD

Literature review current through: Dec 2017. | **This topic last updated:** Nov 30, 2017.

Transition from pediatric to adult care: Sickle cell disease

Author: Marsha J Treadwell, PhD

Literature review current through: Dec 2017. | **This topic last updated:** Jan 18, 2018.

The acute chest syndrome in children and adolescents with sickle cell disease

Authors: Matthew Heeney, MD; Donald H Mahoney, Jr, MD

Literature review current through: Dec 2017. | **This topic last updated:** Dec 18, 2017.

Prevention of stroke (initial or recurrent) in sickle cell disease

Author: Alex George, MD, PhD

Literature review current through: Dec 2017. | **This topic last updated:** Oct 26, 2017.

Vaso-occlusive pain management in sickle cell disease

Authors: Michael R DeBaun, MD, MPH; Elliott P Vichinsky, MD

Literature review current through: Dec 2017. | **This topic last updated:** Nov 30, 2017.

Hydroxyurea use in sickle cell disease

Authors: Griffin P Rodgers, MD; Alex George, MD, PhD

Literature review current through: Dec 2017. | **This topic last updated:** Dec 04, 2017.

Clinical manifestations and diagnosis of the thalassemias

Author: Edward J Benz, Jr, MD

Literature review current through: Dec 2017. | **This topic last updated:** Jan 08, 2018.

Management and prognosis of the thalassemias

Author: Edward J Benz, Jr, MD

Literature review current through: Dec 2017. | **This topic last updated:** Dec 06, 2017.

Hematopoietic cell transplantation for transfusion-dependent thalassemia

Author: Emanuele Angelucci, MD

Literature review current through: Dec 2017. | **This topic last updated:** Dec 18, 2017.

Methods for hemoglobin analysis and hemoglobinopathy testing

Author: Carolyn Hoppe, MD

Literature review current through: Dec 2017. | **This topic last updated:** Jan 09, 2018.

Prenatal screening and testing for hemoglobinopathy

Author: Amber M Yates, MD

Literature review current through: Dec 2017. | **This topic last updated:** Jan 09, 2018.

Approach to the adult patient with anemia

Author: Stanley L Schrier, MD

Literature review current through: Dec 2017. | **This topic last updated:** Dec 06, 2017.

Congenital and acquired disorders of platelet function

Author: Steven Coutre, MD

Literature review current through: Dec 2017. | **This topic last updated:** Sep 07, 2017.

Approach to the adult with unexplained thrombocytopenia

Authors: James N George, MD; Donald M Arnold, MD, MSc

Literature review current through: Dec 2017. | **This topic last updated:** Dec 28, 2017.

Causes of thrombocytopenia in children

Author: Donald L Yee, MD

Literature review current through: Dec 2017. | **This topic last updated:** Nov 10, 2017.

New England Journal of Medicine

Sickle Cell Disease
Piel FB, Steinberg MH, Rees DC.
April 20, 2017
N Engl J Med 2017; 376:1561-1573

Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease
Ataga KI, Kutlar A, Kanter J et al.
February 2, 2017
N Engl J Med 2017; 376:429-439

Sickle Cell Disease — A History of Progress and Peril
Wailoo K.
March 2, 2017
N Engl J Med 2017; 376:805-807

Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

Maude SL, Laetsch TW, Buechner J et al.
February 1, 2018
N Engl J Med 2018; 378:439-448

Long-Term Follow-up of CD19 CAR Therapy in Acute Lymphoblastic Leukemia
Park JH, Rivière I, Gonen M et al.
February 1, 2018
N Engl J Med 2018; 378:449-459

Brentuximab Vedotin with Chemotherapy for Stage III or IV Hodgkin's Lymphoma
Connors JM, Jurczak W, Straus DJ et al.
January 25, 2018
N Engl J Med 2018; 378:331-344

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Recent Database Articles

Below is a selection of articles recently added to the healthcare databases on red cell and platelet disorders, focusing this month on sickle cell. If you would like any of the articles in full text, or if you would like a more focused search on your own topic, please contact us: library@bristol.nhs.uk

Sickle Cell

1. Evidence-Based Practice Standard Care for Acute Pain Management in Adults With Sickle Cell Disease in an Urgent Care Center.

Author(s): Kim, Sunghee; Brathwaite, Ron; Kim, Ook

Source: Quality management in health care; ; vol. 26 (no. 2); p. 108-115

Publication Type(s): Journal Article

Available at Quality management in health care - from nih.gov

Abstract:BACKGROUNDVaso-occlusive episodes (VOEs) with sickle cell disease (SCD) require opioid treatment. Despite evidence to support rapid pain management within 30 minutes, care for these patients does not consistently meet this benchmark. This quality improvement study sought to decrease the first analgesic administration time, increase patient satisfaction, and expedite patient flow.METHODSA prospective pre-/postevaluation design was used to evaluate outcomes with patients 18 years or older with VOEs in an urgent care (UC) center after implementation of evidence-based practice standard care (EBPSC). A pre- and postevaluation survey of SCD patients' satisfaction with care and analogous surveys of the UC team to assess awareness of EBPSC were used. A retrospective review of the electronic medical records of patients with VOEs compared mean waiting time from triage to the first analgesic administration and the mean length of stay (LOS) over 6 months.RESULTSImplementing EBPSC decreased the mean time of the first analgesic administration (P = .001), significantly increased patient satisfaction (P = .002), and decreased the mean LOS (P = .010).CONCLUSIONImplementing EBPSC is a crucial step for improving the management of VOEs and creating a positive patient experience. The intervention enhances the quality of care for the SCD population in a UC center.

2. Stigma and illness uncertainty: adding to the burden of sickle cell disease.

Author(s): Blake, Alphanso; Asnani, Vikram; Leger, Robin R; Harris, June; Odesina, Victoria; Hemmings, Daileann L; Morris, Denise A; Knight-Madden, Jennifer; Wagner, Linda; Asnani, Monika Rani

Source: Hematology (Amsterdam, Netherlands); Mar 2018; vol. 23 (no. 2); p. 122-130

Publication Type(s): Journal Article

Available at Hematology (Amsterdam, Netherlands) - from EBSCO (MEDLINE Complete)

Abstract:BACKGROUNDPersons with sickle cell disease (SCD) experience multiple medical and physical complications; the disease also has numerous effects on their social and emotional well-being. We hypothesized that adults with SCD in Jamaica experience moderate levels of stigma and

illness uncertainty and that these experiences may be associated with socio-demographic factors, such as gender, educational status and economic status.METHODSWe surveyed 101 adults with SCD (54.5% female; mean age 31.6 ± 10.4 years; 72.2% homozygous SCD) using the Stigma in Sickle Cell Disease Scale (Adult), Mishel Uncertainty in Illness Scale (Adult) and a Socio-Demographic questionnaire.RESULTSThe mean stigma score was 33.6 ± 21.6 (range: 2-91) with no significant difference between males and females (32.3 ± 21.3 vs. 34.7 ± 21.9; p-value = 0.58). Illness uncertainty was greater in females than in males, though not statistically significant, (88.7 ± 13.5 vs. 82.6 ± 19.2; p-value: 0.07). Stigma and uncertainty had a significant positive correlation (r: 0.31; p-value: 0.01). In an age and sex controlled model, stigma scores were lower with higher numbers of household items (coef: -2.26; p-value: 0.001) and higher in those living in greater crowding (coef: 7.89; p-value: 0.002). Illness uncertainty was higher in females (coef: 6.94; p-value: 0.02) and lower with tertiary as compared with primary education (coef: -16.68; p-value: 0.03).CONCLUSIONThe study highlights socioeconomic factors to be significant to the stigma and illness uncertainty experiences in SCD. Efforts by healthcare workers to reduce patient illness uncertainty may have additional impact, reducing their stigma.

3. Ethical Challenges in Hematopoietic Cell Transplantation for Sickle Cell Disease.

Author(s): Nickel, Robert Sheppard; Kamani, Naynesh R

Source: Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation; Feb 2018; vol. 24 (no. 2); p. 219-227

Publication Type(s): Journal Article Review

Abstract: Hematopoietic cell transplantation (HCT) using an HLA-identical sibling donor offers a very high likelihood of cure with good outcomes for patients with sickle cell disease (SCD), and alternative donor HCT for SCD is an area of active clinical research. Thus, HCT is a potential option for a growing number of patients with SCD. This expanded use of HCT has raised several ethical questions. Who is eligible for HCT, in terms of both disease severity and psychosocial factors? Should affected children with matched sibling donors undergo HCT only when they have declared themselves as having significant symptomatology? Regarding donors, special ethical challenges include the use of preimplantation genetic diagnosis to conceive an HLA-identical sibling. In this review, we critically analyze various ethical challenges related to HCT for SCD, and offer recommendations to guide clinical care.

4. A randomized controlled trial comparing two vaso-occlusive episode (VOE) protocols in sickle cell disease (SCD).

Author(s): Tanabe, Paula; Silva, Susan; Bosworth, Hayden B; Crawford, Regina; Paice, Judith A; Richardson, Lynne D; Miller, Christopher N; Glassberg, Jeffrey

Source: American journal of hematology; Feb 2018; vol. 93 (no. 2); p. 159-168

Publication Type(s): Journal Article

Abstract: Limited evidence guides opioid dosing strategies for acute Sickle Cell (SCD) pain. We compared two National Heart, Lung and Blood (NHBLI) recommended opioid dosing strategies (weight-based vs. patient-specific) for ED treatment of acute vaso-occlusive episodes (VOE). A prospective randomized controlled trial (RCT) was conducted in two ED's. Adults ≥ 21 years of age with SCD disease were eligible. Among the 155 eligible patients, 106 consented and 52 had eligible visits. Patients were pre-enrolled in the outpatient setting and randomized to one of two opioid dosing strategies for a future ED visit. ED providers accessed protocols through the electronic medical record. Change in pain score (0-100 mm VAS) from arrival to ED disposition, as well as side

effects were assessed. 52 patients (median age was 27 years, 42% were female, and 89% black) had one or more ED visits for a VOE (total of 126 ED study visits, up to 5 visits/patient were included). Participants randomized to the patient-specific protocol experienced a mean reduction in pain score that was 16.6 points greater than patients randomized to the weight-based group (mean difference 95% CI = 11.3 to 21.9, P = 0.03). Naloxone was not required for either protocol and nausea and/or vomiting was observed less often in the patient-specific protocol (25.8% vs 59.4%, P = 0.0001). The hospital admission rate for VOE was lower for patients in the patient-specific protocol (40.3% vs 57.8% P = 0.05). NHLBI guideline-based analgesia with patient-specific opioid dosing resulted in greater improvements in the pain experience compared to a weight-based strategy, without increased side effects.

5. Desire for parenthood and reproductive health knowledge in adolescents and young adults with sickle cell disease and their caregivers.

Author(s): Nahata, Leena; Caltabellotta, Nicole M; Ball, Kyle; O'Brien, Sarah H; Creary, Susan E

Source: Pediatric blood & cancer; Feb 2018; vol. 65 (no. 2)

Publication Type(s): Clinical Trial Journal Article

Abstract:BACKGROUND/OBJECTIVESickle cell disease (SCD) and hydroxyurea have implications for fertility and reproductive health. The goal of this study was to examine desire for parenthood and reproductive health knowledge among a cohort of adolescent and young adult (AYA) with SCD receiving hydroxyurea and their caregivers at a large pediatric academic center.METHODSPatients with SCD were approached from September 2016 to July 2017 if they were: (1) 12-20 years old, (2) prescribed hydroxyurea for at least 6 months, (3) proficient in English, and (4) accompanied by a caregiver who was proficient in English and willing to participate. Participants self-reported sociodemographic characteristics and completed surveys to assess their/their child's desire for parenthood and other life goals, and reproductive health knowledge.RESULTSEighteen patient-caregiver dyads completed the study (78.3% of those eligible); 61.1% indicated that they wanted to have future biological children. Few participants reported receiving information about fertility (16.7% of AYA and 27.8% of caregivers) or birth control (11.1% of AYA and 22.2% of caregivers) from their/their child's health care provider, and the majority had received no information on these topics. Less than half of participants reported that SCD (22.2% of AYA and 50.0% of caregivers) or hydroxyurea (11.1% of AYA and 27.8% of parents) could potentially impair fertility.CONCLUSIONSBiological parenthood was important to this cohort yet fertility and reproductive health knowledge was low, suggesting that clinicians should prioritize conversations about infertility risk and birth control options with AYA with SCD on hydroxyurea and their caregivers. More research is needed to identify optimal approaches to these discussions.

6. Implications of a paediatrician-psychologist tandem for sickle cell disease care and impact on cognitive functioning.

Author(s): Lerner, Adrienne; Picard, Hervé; May, Adrien; Gajdos, Vincent; Malou-Dhaussy, Louise; Maroja-Cox, Flaviana; Salomon, Laurence; Odièvre, Marie-Hélène

Source: European journal of pediatrics; Feb 2018; vol. 177 (no. 2); p. 193-203

Publication Type(s): Journal Article

Abstract: Sickle cell disease (SCD), a life-threatening chronic disease, necessitates a paediatric treatment plan that considers the influence of psychological, family and intercultural factors. At the Louis-Mourier Hospital (APHP) in Colombes, France, we introduced an original paediatric-psychological partnership where a clinical psychologist accompanies the paediatrician at

programmed consultations. We evaluated children and their parents treated in Colombes and in two other paediatric units using standardized culture-free tools and clinical interviews to evaluate the psychological repercussions of SCD. We first present a global view of the different ways that SCD affects both children and their families. We then discuss findings from a study evaluating the overall efficacy of an integrated psycho-medical treatment model as compared to the usual medical care model. Children in the integrated care model improved their cognitive functioning assessed using the Rey-Osterrieth complex figure test compared to treatment as usual.CONCLUSIONFindings suggest that the concept of a "partnership practice" can improve children's ability to grapple with SCD and is a promising approach for long-term care of SCD. What is Known: • Painful crises of sickle cell disease are unpredictable and appear in early childhood • Stress as well as the complex psychological and intercultural issues associated with SCD may aggravate the children's symptoms • Standard pediatric care and research deal primarily with medical issues What is New: • Evidence-based research examining the psychological repercussions of SCD in pediatric treatment as well as the parental distress • First study using standardized culture-free tools • Cognitive functioning improves under an innovative "partnership" model.

7. Intracranial 4D flow magnetic resonance imaging reveals altered haemodynamics in sickle cell disease.

Author(s): Václavů, Lena; Baldew, Zelonna A V; Gevers, Sanna; Mutsaerts, Henri J M M; Fijnvandraat, Karin; Cnossen, Marjon H; Majoie, Charles B; Wood, John C; VanBavel, Ed; Biemond, Bart J; van Ooij, Pim; Nederveen, Aart J

Source: British journal of haematology; Feb 2018; vol. 180 (no. 3); p. 432-442

Publication Type(s): Journal Article

Abstract: Stroke risk in children with sickle cell disease (SCD) is currently assessed with routine transcranial Doppler ultrasound (TCD) measurements of blood velocity in the Circle of Willis (CoW). However, there is currently no biomarker with proven prognostic value in adult patients. Four-dimensional (4D) flow magnetic resonance imaging (MRI) may improve risk profiling based on intracranial haemodynamics. We conducted neurovascular 4D flow MRI and blood sampling in 69 SCD patients [median age 15 years (interquartile range, IQR: 12-50)] and 14 healthy controls [median age 21 years (IQR: 18-43)]. We measured velocity, flow, lumen area and endothelial shear stress (ESS) in the CoW. SCD patients had lower haematocrit and viscosity, and higher velocity, flow and lumen area, with lower ESS compared to healthy controls. We observed significant age-related decline in haemodynamic 4D flow parameters; velocity (Spearman's ρ = -0·36 to -0·61), flow (ρ = -0·26 to -0·52) and ESS (ρ = -0·14 to -0·54) in SCD patients. Further analysis in only adults showed that velocity values were similar in SCD patients compared to healthy controls, but that the additional 4D flow parameters, flow and lumen area, were higher, and ESS lower, in the SCD group. Our data suggest that 4D flow MRI may identify adult patients with an increased stroke risk more accurately than current TCD-based velocity.

8. Fetal haemoglobin induction in sickle cell disease.

Author(s): Paikari, Alireza; Sheehan, Vivien A

Source: British journal of haematology; Jan 2018; vol. 180 (no. 2); p. 189-200

Publication Type(s): Journal Article Review

Abstract: Fetal haemoglobin (HbF, α2γ2) induction has long been an area of investigation, as it is known to ameliorate the clinical complications of sickle cell disease (SCD). Progress in identifying novel HbF-inducing strategies has been stymied by limited understanding of gamma (γ)-globin

regulation. Genome-wide association studies (GWAS) have identified variants in BCL11A and HBS1L-MYB that are associated with HbF levels. Functional studies have established the roles of BCL11A, MYB, and KLF1 in γ-globin regulation, but this information has not yielded new pharmacological agents. Several drugs are under investigation in clinical trials as HbF-inducing agents, but hydroxycarbamide remains the only widely used pharmacologic therapy for SCD. Autologous transplant of edited haematopoietic stem cells holds promise as a cure for SCD, either through HbF induction or correction of the causative mutation, but several technical and safety hurdles must be overcome before this therapy can be offered widely, and pharmacological therapies are still needed.

9. Sickle cell disease: a malady beyond a hemoglobin defect in cerebrovascular disease.

Author(s): Ansari, Junaid; Moufarrej, Youmna E; Pawlinski, Rafal; Gavins, Felicity N E

Source: Expert review of hematology; Jan 2018; vol. 11 (no. 1); p. 45-55

Publication Type(s): Journal Article

Abstract:INTRODUCTIONSickle cell disease (SCD) is a devastating monogenic disorder that presents as a multisystem illness and affects approximately 100,000 individuals in the United States alone. SCD management largely focuses on primary prevention, symptomatic treatment and targeting of hemoglobin polymerization and red blood cell sickling. Areas covered: This review will discuss the progress of SCD over the last few decades, highlighting some of the clinical (mainly cerebrovascular) and psychosocial challenges of SCD in the United States. In addition, focus will also be made on the evolving science and management of this inherited disease. Expert commentary: Until recently hydroxyurea (HU) has been the only FDA approved therapy for SCD. However, advancing understanding of SCD pathophysiology has led to multiple clinical trials targeting SCD related thrombo-inflammation, abnormal endothelial biology, increased oxidant stress and sickle cell mutation. Yet, despite advancing understanding, available therapies are limited. SCD also imposes great psychosocial challenges for the individual and the affected community, which has previously been under-recognized. This has created a pressing need for complementary adjuvant therapies with repurposed and novel drugs, in addition to the establishment of comprehensive clinics focusing on both the medical treatment and the psychosocial issues associated with SCD.

10. Recurrent Acute Chest Syndrome in Pediatric Sickle Cell Disease: Clinical Features and Risk Factors.

Author(s): Patterson, Gaylen D; Mashegu, Hafsat; Rutherford, Jordan; Seals, Samantha; Josey, David; Karlson, Cynthia; McNaull, Melissa; May, Warren; Carroll, Clinton; Barr, Frederick E; Majumdar, Suvankar

Source: Journal of pediatric hematology/oncology; Jan 2018; vol. 40 (no. 1); p. 51-55

Publication Type(s): Journal Article

Abstract: Acute chest syndrome (ACS) is a common and serious lung complication in sickle cell disease. A retrospective medical chart review was performed over a 6-year period in all pediatric ACS patients to investigate whether factors during the initial hospitalization were associated with recurrent ACS episodes. There were 386 episodes of ACS: 149 had only 1 episode of ACS, and 76 had >1 episode of ACS; 172 (76.4%) had hemoglobin SS, and 39 (17.3%) had hemoglobin SC. The most common presenting features were fever (83%), pain (70%), and cough (61%), which changed with the number of ACS episodes. Children <4 years old were at greatest risk of recurrent ACS (P=0.018). In addition, history of asthma (adjusted incident rate ratio [IRR]=1.52; 95% confidence interval [CI], 1.22-1.98; P<0.0001), shortness of breath (IRR, 1.29; 95% CI, 1.02-1.62; P=0.033), and length of hospital stay (IRR, 1.04; 95% CI, 1.01-1.08; P=0.017) were significantly associated with prospective

ACS events. Multiple episodes of ACS are common in sickle cell disease, and certain risk factors during the initial hospitalization are associated with recurrent ACS.

11. Predicting changes in hemoglobin S after simple transfusion using complete blood counts.

Author(s): Mathur, Gagan; Ten Eyck, Patrick; Knudson, C Michael

Source: Transfusion; Jan 2018; vol. 58 (no. 1); p. 138-144

Publication Type(s): Journal Article

Abstract:BACKGROUNDHemoglobin S percentages are used in the management of patients who have sickle cell disease. However, hemoglobin S measurements often are not routinely or rapidly performed. Rapid and accurate methods to estimate hemoglobin S levels after simple transfusion may improve the care of patients with sickle cell disease.STUDY DESIGN AND METHODSA comprehensive review of the electronic medical record identified 24 stable patients with sickle cell disease who received simple red blood cell transfusions and had hemoglobin S measurements before and after the transfusion that were less than 72 hours apart. Examination of these patients identified 62 separate transfusions that met our criteria. Three simple equations that utilized complete blood count values and readily available information from the medical record were used to predict the post-transfusion hemoglobin S level after transfusion (Equation 1: predicted post-transfusion hemoglobin = pre-transfusion hemoglobin S × [pre-transfusion hemoglobin/post-transfusion hemoglobin]; Equation 2: predicted post-transfusion hemoglobin S = pre-transfusion hemoglobin S × [pre-transfusion hematocrit/post-transfusion hematocrit]; and Equation 3: predicted post-transfusion hemoglobin S = pre-transfusion hemoglobin S × total pre-transfusion hemoglobin/[total pre-transfusion hemoglobin + (red blood cell volume × 20)]).RESULTSThe predicted hemoglobin S values for all three equations showed a highly significant correlation with the measured post-hemoglobin S value. The coefficient of determination (R2) for Equations 1, 2, and 3 was 0.95, 0.92, and 0.97, respectively. Predicting the post-transfusion hemoglobin S value using estimates of the patient's total hemoglobin and the transfused hemoglobin (Equation 3) was the most precise.CONCLUSIONReductions in hemoglobin S values in patients with sickle cell disease who receive simple red blood cell transfusions can be reliably predicted using complete blood cell measurements and simple arithmetic equations.

12. Behavioral and Pharmacological Adherence in Pediatric Sickle Cell Disease: Parent-Child Agreement and Family Factors Associated With Adherence.

Author(s): Klitzman, Page H; Carmody, Julia K; Belkin, Mary H; Janicke, David M

Source: Journal of pediatric psychology; Jan 2018; vol. 43 (no. 1); p. 31-39

Publication Type(s): Journal Article

Abstract: ObjectiveThis study aimed to evaluate agreement between children and parents on a measure of behavioral and pharmacological adherence in children with sickle cell disease (SCD), and the associations among family factors (i.e., problem-solving skills, routines, communication) and adherence behaviors.MethodsIn all, 85 children (aged 8-18 years) with SCD and their parents completed questionnaires assessing individual and family factors.ResultsOverall parent-child agreement on an adherence measure was poor, particularly for boys and older children. Greater use of child routines was associated with better overall child-reported adherence. Open family communication was associated with higher overall parent-reported adherence.ConclusionsWhile further research is needed before definitive conclusions can be drawn, results suggest the need to assess child adherence behaviors via both child and parent reports. Findings also suggest that more

daily family routines and open family communication may be protective factors for better disease management.

13. What motivates individuals with sickle cell disease to talk with others about their illness? Reasons for and against sickle cell disease disclosure.

Author(s): Derlega, Valerian J; Maduro, Ralitsa S; Janda, Louis H; Chen, Ian A; Goodman, Benjamin M

Source: Journal of health psychology; Jan 2018; vol. 23 (no. 1); p. 103-113

Publication Type(s): Journal Article

Abstract: This interview study documented how individuals with sickle cell disease make decisions about who to talk with concerning their illness based on psychological and interpersonal issues that are important to them. Reasons for sickle cell disease disclosure to specific persons were self-related (receiving support, venting feelings), other-related (educating others about sickle cell disease, forewarning others about sickle cell disease-related problems, someone asked for information about the disease), or situational (mostly focusing on another person being physically close or available to talk to). Reasons for sickle cell disease nondisclosure to specific persons were self-related (fear of rejection, being stereotyped, maintaining privacy) or other-related (lack of support, not worrying someone).

14. Sickle cell retinopathy: improving care with a multidisciplinary approach.

Author(s): Menaa, Farid; Khan, Barkat Ali; Uzair, Bushra; Menaa, Abder

Source: Journal of multidisciplinary healthcare; 2017; vol. 10 ; p. 335-346

Publication Type(s): Journal Article Review

Available at Journal of multidisciplinary healthcare - from Europe PubMed Central - Open Access

Abstract: Sickle cell retinopathy (SCR) is the most representative ophthalmologic complication of sickle cell disease (SCD), a hemoglobinopathy affecting both adults and children. SCR presents a wide spectrum of manifestations and may even lead to irreversible vision loss if not properly diagnosed and treated at the earliest. Over the past decade, multidisciplinary research developments have focused upon systemic, genetic, and ocular risk factors of SCR, enabling the clinician to better diagnose and manage these patients. In addition, newer imaging and testing modalities, such as spectral domain-optical coherence tomography angiography, have resulted in the detection of subclinical retinopathy related to SCD. Innovative therapy includes intravitreal injection of an anti-vascular endothelial growth factor (eg, Lucentis® [ranibizumab] or Eylea® [aflibercept]) which appears comparatively safe and efficient, and may be combined with laser photocoagulation (LPC) for proliferative SCR. The effect of LPC alone does not significantly lead to the regression of advanced SCR, although it helps in avoiding hemorrhage and sight loss. This comprehensive article is based on 10-years retrospective (2007-2017) studies. It aims to present advances and recommendations in SCR theranostics while pointing out the requirement of combinatorial approaches for better management of SCR patients. To reach this goal, we identified and analyzed randomized original and review articles, clinical trials, non-randomized intervention studies, and observational studies using specified keywords in various databases (eg, Medline, Embase, Cochrane, ClinicalTrials.gov).

15. Current Standards of Care and Long Term Outcomes for Thalassemia and Sickle Cell Disease.

Author(s): Chonat, Satheesh; Quinn, Charles T

Source: Advances in experimental medicine and biology; 2017; vol. 1013 ; p. 59-87

Publication Type(s): Journal Article

Available at Advances in experimental medicine and biology - from nih.gov

Abstract: Thalassemia and sickle cell disease (SCD) are disorders of hemoglobin that affect millions of people worldwide. The carrier states for these diseases arose as common, balanced polymorphisms during human history because they afforded protection against severe forms of malaria. These complex, multisystem diseases are reviewed here with a focus on current standards of clinical management and recent research findings. The importance of a comprehensive, multidisciplinary and lifelong system of care is also emphasized.

16. Adolescents' experiences of living with sickle cell disease: An integrative narrative review of the literature.

Author(s): Poku, Brenda Agyeiwaa; Caress, Ann-Louise; Kirk, Susan

Source: International journal of nursing studies; Dec 2017; vol. 80 ; p. 20-28

Publication Type(s): Journal Article Review

Abstract:BACKGROUNDSickle Cell Disease is the commonest monogenic haemoglobinopathy worldwide. Living with a long-term condition such as sickle cell disease during adolescence constitutes a significant challenge for the key stakeholders due to the combined effects of chronic illness and adolescent development. For adolescents with sickle cell disease to be cared for and supported appropriately and effectively, it is crucial that health professionals have a comprehensive knowledge and understanding of how adolescents experience living with the condition. While there is developing literature about how adolescent's experience sickle cell disease, this body of research has not been critically reviewed and synthesised.OBJECTIVETo identify, critically appraise and synthesise primary research exploring adolescents' experiences of living with sickle cell disease to make recommendations for practice and research.DESIGNIntegrative narrative review.DATA SOURCESA systematic search of 10 electronic databases and key journals was conducted to identify studies from the inception of databases to September 2016.REVIEW METHODInclusion criteria: adolescents with sickle cell disease aged 12-19 years, primary data on adolescents' own perspectives, and published in English. Data were extracted on study contexts, methodology/design, theoretical constructs, participants, and key findings. Findings from included studies were synthesised using the integrative narrative approach. Additionally, the methodological quality of studies was assessed using the Hawker et al. (2002) appraisal checklist.RESULTS683 studies were identified, of which 40 fulfilled the inclusion criteria. Nine broad themes emerged: knowledge and understanding of the condition, symptom experiences, self-management, attitude to treatment, healthcare experiences, social relationships, difference and striving for normality, school experiences, and emotional well-being and coping. Majority of the studies were of moderate quality methodologically. Quality assessment demonstrated a high risk of bias in three studies.CONCLUSIONSSickle cell disease impacts on multiple facets of an adolescent's life. While there are similarities in the experience of living with sickle cell disease and living with other chronic illnesses, there are essential differences in relationship dynamics and healthcare experience. The adolescents expressed less confidence in generic healthcare providers. The review highlights areas relating to symptom management and health service provision that has been under-researched and need further exploration to understand adolescents' experiences and their support needs fully. Nursing care and research should focus more on adolescents' developmental wellbeing, promote peer support network among adolescents with the condition and with adolescents with other chronic illnesses and collaborate with adolescents to ensure service development are developmentally and culturally appropriate.

17. Sleep-disordered breathing in patients with sickle cell disease.

Author(s): Raghunathan, Vikram M; Whitesell, Peter L; Lim, Seah H

Source: Annals of hematology; Dec 2017

Publication Type(s): Journal Article Review

Abstract: Sickle cell disease is one of the most common hereditary hemoglobinopathies worldwide, and its vaso-occlusive and hemolytic crises cause considerable patient morbidity. A growing body of evidence has shown that sleep-disordered breathing, and in particular, obstructive sleep apnea, occurs at high frequency in the sickle cell population, and that there is significant overlap in the underlying pathophysiology of these two conditions. Through a variety of mechanisms including nocturnal hypoxemia and increased oxidative stress, production of pro-inflammatory cytokines, and endothelial dysfunction, sickle cell anemia and sleep-disordered breathing potentiate each other's clinical effects and end-organ complications. Here, we will review the shared pathophysiologic mechanisms of these conditions and discuss their clinical sequelae. We will also examine the results of studies that have been carried out with clinical intervention of nocturnal hypoxemia in patients with sickle cell disease in the attempts to overcome the complications of the disease. Finally, we will propose the areas of investigation that merit further investigations in future in patients with sickle cell disease and sleep-disordered breathing.

18. The spectrum of sickle hemoglobin-related nephropathy: from sickle cell disease to sickle trait.

Author(s): Naik, Rakhi P; Derebail, Vimal K

Source: Expert review of hematology; Dec 2017; vol. 10 (no. 12); p. 1087-1094

Publication Type(s): Journal Article

Abstract:INTRODUCTIONRenal dysfunction is among the most common complication of sickle cell disease (SCD), from hyposthenuria in children to progression to overt chronic kidney disease (CKD) in young adults. Emerging evidence now suggests that sickle hemoglobin-related nephropathy extends to individuals with sickle cell trait (SCT). Areas covered: This review will highlight the pathophysiology, epidemiology, and management recommendations for sickle hemoglobin-related nephropathy in both SCD and SCT. In addition, it will focus on the major demographic and genetic modifiers of renal disease in sickling hemoglobinopathies. Expert commentary: Studies have elucidated the course of renal disease in SCD; however, the scope and age of onset of renal dysfunction in SCT has yet to be determined. In SCD, several modifiers of renal disease - such as α-thalassemia, hemoglobin F, APOL1 and HMOX1 - have been described and provide an opportunity for a precision medicine approach to risk stratify patients who may benefit from early intervention. Extrapolating from this literature may also provide insight into the modifiers of renal disease in SCT. Further studies are needed to determine the optimal treatment for sickle hemoglobin-related nephropathy.

19. Evolving treatment paradigms in sickle cell disease.

Author(s): Jagadeeswaran, Ramasamy; Rivers, Angela

Source: Hematology. American Society of Hematology. Education Program; Dec 2017; vol. 2017 (no. 1); p. 440-446

Publication Type(s): Journal Article Review

Abstract: Sickle cell disease (SCD) is an inheritable hemoglobinopathy characterized by polymerization of hemoglobin S in red blood cells resulting in chronic hemolytic anemia, vaso-occlusive painful crisis, and multiorgan damage. In SCD, an increased reactive oxygen species (ROS) generation occurs both inside the red blood cells and inside the vascular lumen, which augment hemolysis and cellular adhesion. This review discusses the evolving body of literature on the role of ROS in the pathophysiology of SCD as well as some emerging therapeutic approaches to SCD with a focus on the reduction of ROS.

20. How many people have sickle cell disease in the UK?

Author(s): Dormandy, Elizabeth; James, John; Inusa, Baba; Rees, David

Source: Journal of public health (Oxford, England); Dec 2017

Publication Type(s): Journal Article

Abstract: BackgroundSickle Cell Disease (SCD) is now one of the most common serious genetic condition in England. There is no reliable estimate of the total number of people living with SCD in the UK, to support commissioners and providers of services for people with SCD.AimTo obtain reliable data on the total number of people living with SCD in the UK in 2016.MethodInformation was requested from all national databases known to hold information on the number of people living with SCD in the UK. The information from each data source was first reviewed to estimate likely inaccuracies and then combined to provide a best estimate of people living with SCD in the UK.ConclusionThis process indicated there are are about 14000 people living with SCD in the UK. This is equivalent to 1 in 4600 people.

21. Hematopoietic stem cell transplantation for sickle cell disease: The changing landscape.

Author(s): Kassim, Adetola A; Sharma, Deva

Source: Hematology/oncology and stem cell therapy; Dec 2017; vol. 10 (no. 4); p. 259-266

Publication Type(s): Journal Article Review

Abstract: Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only curative therapy for sickle cell disease (SCD); however, its use is limited by lack of suitable human leukocyte antigen (HLA)-matched donors and decreased application in older patients with significant morbidity. Myeloablative, HLA-identical sibling transplantation in children with SCD offers excellent long-term survival, with overall and event-free survival rates of 95% and 92%, respectively. However, the risk of graft-versus-host-disease, infections, infertility, and other long-term transplant complications, further limits its widespread use. Recent approaches using reduced intensity conditioning (RIC) are associated with lower toxicity, allowing extension of this modality to children and adults with significant morbidity; however, these approaches are also associated with increased risk of graft failure. The optimal RIC regimen that strikes the optimal balance between maximizing the rate of stable engraftment while minimizing transplant-related morbidity and mortality is unknown. Alternative donor transplants, most prominently, partial HLA-mismatched related transplants (haploidentical), are being investigated with promising initial results. This review will discuss long-term results of HLA-matched sibling HSCT for SCD, and recent updates on HLA-matched unrelated donor and unrelated umbilical cord blood HSCT for SCD.

22. Acute Chest Syndrome in Children with Sickle Cell Disease.

Author(s): Jain, Shilpa; Bakshi, Nitya; Krishnamurti, Lakshmanan

Source: Pediatric allergy, immunology, and pulmonology; Dec 2017; vol. 30 (no. 4); p. 191-201

Publication Type(s): Journal Article Review

Available at Pediatric allergy, immunology, and pulmonology - from nih.gov

Abstract: Acute chest syndrome (ACS) is a frequent cause of acute lung disease in children with sickle cell disease (SCD). Patients may present with ACS or may develop this complication during the course of a hospitalization for acute vaso-occlusive crises (VOC). ACS is associated with prolonged hospitalization, increased risk of respiratory failure, and the potential for developing chronic lung disease. ACS in SCD is defined as the presence of fever and/or new respiratory symptoms accompanied by the presence of a new pulmonary infiltrate on chest X-ray. The spectrum of clinical manifestations can range from mild respiratory illness to acute respiratory distress syndrome. The presence of severe hypoxemia is a useful predictor of severity and outcome. The etiology of ACS is often multifactorial. One of the proposed mechanisms involves increased adhesion of sickle red cells to pulmonary microvasculature in the presence of hypoxia. Other commonly associated etiologies include infection, pulmonary fat embolism, and infarction. Infection is a common cause in children, whereas adults usually present with pain crises. Several risk factors have been identified in children to be associated with increased incidence of ACS. These include younger age, severe SCD genotypes (SS or Sβ0 thalassemia), lower fetal hemoglobin concentrations, higher steady-state hemoglobin levels, higher steady-state white blood cell counts, history of asthma, and tobacco smoke exposure. Opiate overdose and resulting hypoventilation can also trigger ACS. Prompt diagnosis and management with intravenous fluids, analgesics, aggressive incentive spirometry, supplemental oxygen or respiratory support, antibiotics, and transfusion therapy, are key to the prevention of clinical deterioration. Bronchodilators should be considered if there is history of asthma or in the presence of acute bronchospasm. Treatment with hydroxyurea should be considered for prevention of recurrent episodes. This review evaluates the etiology, pathophysiology, risk factors, clinical presentation of ACS, and preventive and treatment strategies for effective management of ACS.

23. Sleep disordered breathing does not predict acute severe pain episodes in children with sickle cell anemia.

Author(s): Willen, Shaina M; Rodeghier, Mark; Rosen, Carol L; DeBaun, Michael R

Source: American journal of hematology; Dec 2017

Publication Type(s): Journal Article

Abstract: Conflicting evidence has suggested that low mean nocturnal hemoglobin oxygen saturation (SpO2) predicts future hospital days for acute severe pain in children with sickle cell anemia (SCA). In an unselected multicenter prospective cohort study, we tested the hypothesis that either low mean nocturnal SpO2 or high obstructive apnea-hypopnea index (OAHI; the number of obstructive apneas and hypopneas with ≥ 3% desaturation or arousal per hour of sleep) or high oxygen desaturation index (ODI; number of ≥ 3% desaturation from baseline saturation per hour of sleep) is associated with increased incidence rates of pain. A total of 140 children with SCA with a median age of 10.8 years (interquartile range 7.2) were followed for a median of 4.9 years (interquartile range 1.8). Overnight polysomnography evaluations at baseline health exam were measured and adjudicated centrally. Multivariable models created in two steps were included. First, all plausible covariates were included in a screening model. Subsequently, covariates meeting level of statistical significance of P < .20 were included in the final model. Contrary to our hypothesis, higher (but not lower) mean nocturnal SpO2 was associated with higher rates of pain episodes (Incidence rate ratio (IRR) 1.10, 95% CI [1.03-1.18], P = .004). Higher log OAHI did not pass screening criteria. Higher log ODI was not significantly associated with higher rates of pain episodes (IRR 0.93, 95% CI [0.82-1.06],

P = .28). Neither low nocturnal SpO2, higher OAHI, nor higher ODI were associated with clinically relevant increased incidence rates of acute severe pain episodes.

24. Risk of Invasive Pneumococcal Disease in Children with Sickle Cell Disease in England: A National Observational Cohort Study, 2010-2015.

Author(s): Oligbu, Godwin; Collins, Sarah; Sheppard, Carmen; Fry, Norman; Dick, Moira; Streetly, Allison; Ladhani, Shamez

Source: Archives of disease in childhood; Dec 2017

Publication Type(s): Journal Article

Available at Archives of disease in childhood - from BMJ Journals - NHS

Available at Archives of disease in childhood - from BMJ Journals

Abstract:OBJECTIVETo describe the clinical presentation, risk factors, serotype distribution and outcomes of invasive pneumococcal disease (IPD) in children with sickle cell disease (SCD) following the introduction of the 13-valent pneumococcal conjugate vaccine (PCV13) in the UK.DESIGNProspective national newborn screening for SCD and enhanced national IPD surveillance.PARTICIPANTSChildren with SCD born in England between 1 September 2010 and 31 August 2014 who developed laboratory-confirmed IPD by 31 December 2015.MAIN OUTCOMES AND MEASURESRisk of IPD in children with SCD compared with children without SCD during the surveillance period.RESULTSEleven children homozygote for haemoglobin S (HbSS) and one double heterozygote for haemoglobin S and C (HbSC) developed IPD. Septicaemia (n=7) and lower respiratory tract infection (n=4) were the main clinical presentations, and serogroup 15 (not present in PCV13) was responsible for 73% (8/11) of cases. Three children with HbSS (27%) died compared with <5% nationally. Children with HbSS had a 49-fold (95% CI 27 to 89, P<0.001) higher risk of IPD compared with their peers without SCD.CONCLUSIONSChildren with SCD remain at increased risk of IPD despite national newborn screening, early penicillin prophylaxis and high pneumococcal vaccine uptake. They are also more likely to die of their infection compared with their peers without SCD. Most IPD cases are now due to serotypes not covered by PCV13. Healthcare professionals need to work more closely with families with SCD and local communities to emphasise the importance of penicillin prophylaxis, explore barriers, allay misguided beliefs and facilitate rapid access to healthcare.

25. A Standardized Clinical Pathway to Decrease Hospital Admissions Among Febrile Children With Sickle Cell Disease.

Author(s): Ellison, Angela M; Smith Whitley, Kim; Kittick, Marlena; Schast, Aileen; Norris, Cynthia; Hartung, Helge; McKnight, Therese; Coyne, Erin; Lavelle, Jane

Source: Journal of pediatric hematology/oncology; Dec 2017

Publication Type(s): Journal Article

Abstract:BACKGROUND AND OBJECTIVERecurrent hospital admissions for patients with sickle cell disease (SCD) are costly and contribute to a low quality of life for patients. We implemented a clinical pathway to safely discharge SCD patients with fever who are evaluated in the emergency department (ED) of a large tertiary care center.METHODSAn interdisciplinary team of ED and hematology physicians, nurses, and an improvement advisor developed a clinical pathway that identified febrile SCD patients at low risk of serious bacterial infection based on historical, clinical, and laboratory criteria who could be discharged from the ED. Phone follow-up was planned through the use of an automated electronic notification that was sent to an established hematology follow-

up pool at the time of ED discharge. We conducted two "fake front end" trials in the ED to receive feedback on our process before full implementation. A postpathway implementation quality improvement team monitored discharge rates, phone follow-up rates and adverse events.RESULTSIn the first 9 weeks postpathway implementation, 100 SCD patients were evaluated for fever; 84 (24%) met low-risk criteria and were discharged home. This reduction in admission rate has been maintained throughout the 3 years postimplementation. Successful phone follow-up was achieved in all discharged patients within 24 hours and no adverse events were identified.CONCLUSIONSLow-risk febrile patients with SCD can be safely discharged from the ED. An automated notification system within the electronic medical record system can facilitate patient follow-up after ED discharge. Future quality improvement efforts aimed to further reduce admissions in this population should target patients with modifiable risk factors for serious bacterial infection.

26. Parents' pain medication underdosing is associated with more emergency department visits in sickle cell disease.

Author(s): Morrison, Andrea K; Myrvik, Matthew P; Brousseau, David C; Drendel, Amy L; Scott, J Paul; Visotcky, Alexis; Panepinto, Julie A

Source: Pediatric blood & cancer; Dec 2017

Publication Type(s): Journal Article

Abstract:OBJECTIVETo determine the association between health literacy, medication knowledge, and pain treatment skills with emergency department (ED) use of parents of children with sickle cell disease (SCD).METHODSParents of children 1- to 12-years-old with SCD were enrolled. Health literacy was assessed using the Newest Vital Sign. Parents completed a structured interview assessing knowledge of the dosage and frequency of home pain medications and an applied skills task requiring them to dose a prescribed pain medication. Underdosage was defined by too small a dose (dosage error) or too infrequent a dose (frequency error). The association between medication knowledge and applied skills with ED visits for pain over the past year was evaluated using Poisson regression adjusting for genotype.RESULTSOne hundred parent/child pairs were included; 50% of parents had low health literacy. Low health literacy was associated with more underdose frequency errors (38% vs. 19%, P = 0.02) on the skills task. On medication knowledge, underdose dosage errors (adjusted incidence rate ratio [aIRR] 2.0, 95% confidence interval [CI] 1.3-3.0) and underdose frequency errors (aIRR, 1.7, 95% CI 1.2-2.6) were associated with a higher rate of ED visits for pain. On the skills task, underdose dosage errors (aIRR 1.6, 95% CI 1.1-2-.4) and underdose frequency errors were associated with more ED visits (aIRR 1.5, 95% CI 1.1-2.1).CONCLUSIONSFor medication knowledge and skills tasks, children of parents who underdosed pain medication had a higher rate of ED visits for pain. Health literate strategies to improve parents' medication skills may improve pain treatment at home and decrease healthcare utilization.

27. Targeting novel mechanisms of pain in sickle cell disease.

Author(s): Tran, Huy; Gupta, Mihir; Gupta, Kalpna

Source: Hematology. American Society of Hematology. Education Program; Dec 2017; vol. 2017 (no. 1); p. 546-555

Publication Type(s): Journal Article Review

Abstract: Patients with sickle cell disease (SCD) suffer from intense pain that can start during infancy and increase in severity throughout life, leading to hospitalization and poor quality of life. A unique feature of SCD is vaso-occlusive crises (VOCs) characterized by episodic, recurrent, and unpredictable episodes of acute pain. Microvascular obstruction during a VOC leads to impaired

oxygen supply to the periphery and ischemia reperfusion injury, inflammation, oxidative stress, and endothelial dysfunction, all of which may perpetuate a noxious microenvironment leading to pain. In addition to episodic acute pain, patients with SCD also report chronic pain. Current treatment of moderate to severe pain in SCD is mostly reliant upon opioids; however, long-term use of opioids is associated with multiple side effects. This review presents up-to-date developments in our understanding of the pathobiology of pain in SCD. To help focus future research efforts, major gaps in knowledge are identified regarding how sickle pathobiology evokes pain, pathways specific to chronic and acute sickle pain, perception-based targets of "top-down" mechanisms originating from the brain and neuromodulation, and how pain affects the sickle microenvironment and pathophysiology. This review also describes mechanism-based targets that may help develop novel therapeutic and/or preventive strategies to ameliorate pain in SCD.

28. Pain-measurement tools in sickle cell disease: where are we now?

Author(s): Darbari, Deepika S; Brandow, Amanda M

Source: Hematology. American Society of Hematology. Education Program; Dec 2017; vol. 2017 (no. 1); p. 534-541

Publication Type(s): Journal Article Review

Abstract: Pain is a complex multidimensional experience and the most common morbidity in patients with sickle cell disease (SCD). Tools to assess pain can be of use not only to guide pain treatment but also to provide insight into underlying pain neurobiology. Mechanisms of pain in SCD are multifactorial and are not completely elucidated. Although vaso-occlusion of microcirculation by sickled red cells is believed to be the underlying mechanism of acute vaso-occlusive pain, mechanisms for chronic pain and the transition from acute to chronic pain are under investigation. A number of modalities can be used in clinical practice and/or research to capture various dimensions of pain. Selection of a pain-assessment tool should be directed by the purpose of the assessment. Pain-assessment tools, many of which are currently in the early stages of validation, are discussed here. Development and validation of these multimodal tools is crucial for developing improved understanding of SCD pain and its management.

29. Optimizing the care model for an uncomplicated acute pain episode in sickle cell disease.

Author(s): Telfer, Paul; Kaya, Banu

Source: Hematology. American Society of Hematology. Education Program; Dec 2017; vol. 2017 (no. 1); p. 525-533

Publication Type(s): Journal Article Review

Abstract: The pathophysiology, clinical presentation, and natural history of acute pain in sickle cell disease are unique and require a disease-centered approach that also applies general principles of acute and chronic pain management. The majority of acute pain episodes are managed at home without the need to access health care. The long-term consequences of poorly treated acute pain include chronic pain, adverse effects of chronic opioid usage, psychological maladjustment, poor quality of life, and excessive health care utilization. There is no standard protocol for management of an acute pain crisis in either the hospital or the community. The assumptions that severe acute pain must be managed in the hospital with parenteral opioids and that strong opioids are needed for home management of pain need to be questioned. Pain management in the emergency department often does not meet acceptable standards, while chronic use of strong opioids is likely to result in opioid-induced hyperalgesia, exacerbation of chronic pain symptoms, and opioid dependency. We suggest that an integrated approach is needed to control the underlying condition, modify

psychological responses, optimize social support, and ensure that health care services provide safe, effective, and prompt treatment of acute pain and appropriate management of chronic pain. This integrated approach should begin at an early age and continue through the adolescent, transition, and adult phases of the care model.

30. Cardiovascular complications in patients with sickle cell disease.

Author(s): Gladwin, Mark T

Source: Hematology. American Society of Hematology. Education Program; Dec 2017; vol. 2017 (no. 1); p. 423-430

Publication Type(s): Journal Article Review

Abstract: Sickle cell disease (SCD) is an autosomal recessive disease in which homozygosity for a single point mutation in the gene encoding the β-globin chain produces hemoglobin S molecules that polymerize within the erythrocyte during deoxygenation; the result is sustained hemolytic anemia and vaso-occlusive events. As patients live to adulthood, the chronic impact of sustained hemolytic anemia and episodic vaso-occlusive episodes leads to progressive end-organ complications. This scenario culminates in the development of 1 or more major cardiovascular complications of SCD for which there are no approved or consensus therapies. These complications include elevated pulmonary artery systolic pressure, pulmonary hypertension, left ventricular diastolic heart disease, dysrhythmia, sudden death, and chronic kidney disease with associated proteinuria, microalbuminuria, and hemoglobinuria. In patients with advancing age, cardiopulmonary organ dysfunction and chronic kidney injury have significant effects on morbidity and premature mortality. Over the last 15 years, a number of tests have been validated in multiple replicate cohort studies that identify patients with SCD at the highest risk of experiencing pulmonary and systemic vasculopathy and death, providing for screening strategies tied to targeted, more aggressive diagnostic and therapeutic interventions.

31. Improving Emergency Department-Based Care of Sickle Cell Pain.

Author(s): Glassberg, Jeffrey A

Source: Hematology. American Society of Hematology. Education Program; Dec 2017; vol. 2017 (no. 1); p. 412-417

Publication Type(s): Journal Article Review

Abstract: Pain is the leading cause of emergency department (ED) visits for individuals living with sickle cell disease (SCD). The care that is delivered in the ED is often cited by patients with SCD as the area of health care in greatest need of improvement. In 2014, the National Heart, Lung, and Blood Institute released guidelines for the care of SCD, including recommendations for the management of acute sickle cell pain in the ED. These guidelines provide a framework to understand the elements of ideal emergency sickle cell pain care; however, they do not provide guidance on barriers and facilitators to achieving these ideals in the complex system of the ED. Presented in this article are 4 tenets of implementing guideline-adherent emergency sickle cell care gleaned from the available literature and continuous quality improvement efforts at our institution. These include: (1) strategies to reduce negative provider attitudes toward patients with SCD; (2) strategies to reduce time-to-first-dose of analgesic medication; (3) strategies to improve ED pain care beyond the first dose of medication; and (4) strategies to improve ED patient safety. Application of the principles discussed within can improve patient and provider satisfaction, quality, and safety.

32. Five lessons learned about long-term pain management in adults with sickle cell disease.

Author(s): Field, Joshua J

Source: Hematology. American Society of Hematology. Education Program; Dec 2017; vol. 2017 (no. 1); p. 406-411

Publication Type(s): Journal Article Review

Abstract: Chronic pain affects one-half of adults with sickle cell disease (SCD). Despite the prevalence of chronic pain, few studies have been performed to determine the best practices for this patient population. Although the pathophysiology of chronic pain in SCD may be different from other chronic pain syndromes, many of the guidelines outlined in the pain literature and elsewhere are applicable; some were consensus-adopted in the 2014 National Heart, Lung, and Blood Institute SCD Guidelines. Recommended practices, such as controlled substance agreements and monitoring of urine, may seem unnecessary or counterproductive to hematologists. After all, SCD is a severe pain disorder with a clear indication for opioids, and mistrust is already a major issue. The problem, however, is not with a particular disease but with the medicines, leading many US states to pass broad legislation in attempts to curb opioid misuse. These regulations and other key tenets of chronic pain management are not meant to deprive adults with SCD of appropriate therapies, and their implementation into hematology clinics should not affect patient-provider relationships. They simply encourage prudent prescribing practices and discourage misuse, and should be seen as an opportunity to more effectively manage our patient's pain in the safest manner possible. In line with guideline recommendations as well as newer legislation, we present five lessons learned. These lessons form the basis for our model to manage chronic pain in adults with SCD.

33. Perinatal and Neonatal Implications of Sickle Cell Disease.

Author(s): Phillips, Cathi; Boyd, Margaret Peggy

Source: Nursing for women's health; Dec 2017; vol. 21 (no. 6); p. 474-487

Publication Type(s): Journal Article

Abstract: Sickle cell disease is the genetic disorder most commonly detected with state-mandated newborn screening. Women with sickle cell disease struggle with psychosocial, emotional, and physical challenges throughout their lives. Pregnancy for women with sickle cell disease brings greater risk for maternal and fetal morbidity and mortality and increased likelihood of hospitalization for complications, including sickle cell pain crisis. Chronic maternal opioid use for pain can place newborns at risk for neonatal abstinence syndrome. Care of a pregnant woman with sickle cell disease requires a collaborative, multidisciplinary team addressing the medical, social, and emotional needs of the woman and her family.

34. Preferences for prenatal diagnosis of sickle-cell disorder: A discrete choice experiment comparing potential service users and health-care providers.

Author(s): Hill, Melissa; Oteng-Ntim, Eugene; Forya, Frida; Petrou, Mary; Morris, Stephen; Chitty, Lyn S

Source: Health expectations : an international journal of public participation in health care and health policy; Dec 2017; vol. 20 (no. 6); p. 1289-1295

Publication Type(s): Journal Article

Available at Health expectations : an international journal of public participation in health care and health policy - from EBSCO (CINAHL with Full Text)

Available at Health expectations : an international journal of public participation in health care and health policy - from EBSCO (MEDLINE Complete)

Available at Health expectations : an international journal of public participation in health care and health policy - from nih.gov

Abstract:BACKGROUNDNon-invasive prenatal diagnosis (NIPD) for sickle-cell disorder (SCD) is moving closer to implementation and studies considering stakeholder preferences are required to underpin strategies for offering NIPD in clinical practice.OBJECTIVEDetermine service user and provider preferences for key attributes of prenatal diagnostic tests for SCD and examine views on NIPD.METHODA questionnaire that includes a discrete choice experiment was used to determine the preferences of service users and providers for prenatal tests that varied across three attributes: accuracy, time of test and risk of miscarriage.RESULTSAdults who were carriers of SCD or affected with the condition (N=67) were recruited from haemoglobinopathy clinics at two maternity units. Health professionals, predominately midwives, who offer antenatal care (N=62) were recruited from one maternity unit. No miscarriage risk was a key driver of decision making for both service users and providers. Service providers placed greater emphasis on accuracy than service users. Current uptake of invasive tests was 63%, whilst predicted uptake of NIPD was 93.8%. Many service users (55.4%) and providers (52.5%) think pressure to have prenatal testing will increase when NIPD for SCD becomes available.CONCLUSIONSThere are clear differences between service users and health professionals' preferences for prenatal tests for sickle-cell disorder. The safety of NIPD is welcomed by parents and uptake is likely to be high. To promote informed choice, pretest counselling should be balanced and not exclusively focused on test safety. Counselling strategies that are sensitive to feelings of pressure to test will be essential.

35. Immunohaematological complications in patients with sickle cell disease after haemopoietic progenitor cell transplantation: a prospective, single-centre, observational study.

Author(s): Allen, Elizabeth S; Srivastava, Kshitij; Hsieh, Matthew M; Fitzhugh, Courtney D; Klein, Harvey G; Tisdale, John F; Flegel, Willy A

Source: The Lancet. Haematology; Nov 2017; vol. 4 (no. 11); p. e553

Publication Type(s): Journal Article

Abstract:BACKGROUNDHaemopoietic progenitor cell (HPC) transplantation can cure sickle cell disease. Non-myeloablative conditioning typically results in donor-derived erythrocytes and stable mixed chimerism of recipient-derived and donor-derived leucocytes. Exposure to donor antigens from the HPC graft and new red cell antibodies induced by transfusion can lead to immunohaematological complications. We assessed the incidence of such complications among HPC transplant recipients with sickle cell disease.METHODSThe study population was all patients with sickle cell disease enrolled before March 31, 2015, in the three clinical trials of non-myeloablative HPC transplantation at the National Institutes of Health. We assessed formation of new red cell antibodies after transplantation and red cell incompatibility between donors and recipients.FINDINGS61 patients were enrolled, 42 were HLA matched and 19 were haploidentical. Nine (15%) had immunohaematological complications. Before HPC transplantation, three patients had antibodies incompatible with their donors. After HPC transplantation, new red cell antibodies were seen in six patients (11 alloantibodies and two autoantibodies), among whom three developed antibodies incompatible with donor or recipient red cells and three developed compatible antibodies. The clinical course of complications was highly variable, from no severe effects attributable to antibodies, to sustained reticulocytopenia, to near-fatal haemolysis. We found no

significant correlation between immunohaematological complications and graft failure, graft rejection, or death.INTERPRETATIONClinical effects ranged from seemingly not clinically important to potentially fatal. In patients with sickle cell disease, donor and recipient red cell phenotypes should be carefully assessed before transplantation to minimise and manage the risk of immunohaematological complications.FUNDINGIntramural Research Program and National Institutes of Health.

36. Sickle cell disease and the eye.

Author(s): Do, Brian K; Rodger, Damien C

Source: Current opinion in ophthalmology; Nov 2017; vol. 28 (no. 6); p. 623-628

Publication Type(s): Journal Article Review

Abstract:PURPOSE OF REVIEWTo review recent literature pertaining to sickle cell retinopathy (SCR) and, in particular, sickle cell maculopathy.RECENT FINDINGSSeveral recent studies suggest that macular perfusion abnormalities seen in patients with sickle cell disease of various genotypes may affect both the superficial and deep capillary plexi, with a predilection for the deep capillary plexus. Further, these changes may be associated with areas of macular thinning, as well as with peripheral retinal ischemia, even in individuals without visual symptoms, contrary to what has previously been described in both diabetic retinopathy and retinal vein occlusion. Several cases also suggest that paracentral acute middle maculopathy may be the pathophysiologic mechanism by which microvascular occlusion leads to macular thinning.SUMMARYSickle cell disease can manifest in a number of ways within the orbit as well as intraocularly because of its nonspecific vasoocclusive episodes. However, SCR is the most common ophthalmic manifestation of this disease. Historically, SCR has been considered a peripheral retinopathy, but the development and use of spectral-domain optical coherence tomography and optical coherence tomography angiography suggest that significant macular vascular changes occur early in this disease, even in asymptomatic individuals.

37. New Ways to Detect Pediatric Sickle Cell Retinopathy: A Comprehensive Review.

Author(s): Pahl, Daniel A; Green, Nancy S; Bhatia, Monica; Chen, Royce W S

Source: Journal of pediatric hematology/oncology; Nov 2017; vol. 39 (no. 8); p. 618-625

Publication Type(s): Meta-analysis Journal Article Review

Abstract: Sickle retinopathy reflects disease-related vascular injury of the eye, which can potentially result in visual loss from vitreous hemorrhage or retinal detachment. Here we review sickle retinopathy among children with sickle cell disease, describe the epidemiology, pediatric risk factors, pathophysiology, ocular findings, and treatment. Newer, more sensitive ophthalmological imaging modalities are available for retinal imaging, including ultra-widefield fluorescein angiography, spectral-domain optical coherence tomography, and optical coherence tomography angiography. Optical coherence tomography angiography provides a noninvasive view of retinal vascular layers that could previously not be imaged and can be quantified for comparative or prospective analyses. Ultra-widefield fluorescein angiography provides a more comprehensive view of the peripheral retina than traditional imaging techniques. Screening for retinopathy by standard fundoscopic imaging modalities detects a prevalence of approximately 10%. In contrast, these more sensitive methods allow for more sensitive examination that includes the retina perimeter where sickle retinopathy is often first detectable. Use of these new imaging modalities may detect a higher prevalence of early sickle pathology among children than has previously been reported. Earlier detection may help in better understanding the pathogenesis of sickle retinopathy and guide future screening and treatment paradigms.

38. Clinical risks and healthcare utilization of hematopoietic cell transplantation for sickle cell disease in the USA using merged databases.

Author(s): Arnold, Staci D; Brazauskas, Ruta; He, Naya; Li, Yimei; Aplenc, Richard; Jin, Zhezhen; Hall, Matt; Atsuta, Yoshiko; Dalal, Jignesh; Hahn, Theresa; Khera, Nandita; Bonfim, Carmem; Majhail, Navneet S; Diaz, Miguel Angel; Freytes, Cesar O; Wood, William A; Savani, Bipin N; Kamble, Rammurti T; Parsons, Susan; Ahmed, Ibrahim; Sullivan, Keith; Beattie, Sara; Dandoy, Christopher; Munker, Reinhold; Marino, Susana; Bitan, Menachem; Abdel-Azim, Hisham; Aljurf, Mahmoud; Olsson, Richard F; Joshi, Sarita; Buchbinder, Dave; Eckrich, Michael J; Hashmi, Shahrukh; Lazarus, Hillard; Marks, David I; Steinberg, Amir; Saad, Ayman; Gergis, Usama; Krishnamurti, Lakshmanan; Abraham, Allistair; Rangarajan, Hemalatha G; Walters, Mark; Lipscomb, Joseph; Saber, Wael; Satwani, Prakash

Source: Haematologica; Nov 2017; vol. 102 (no. 11); p. 1823-1832

Publication Type(s): Journal Article

Abstract: Advances in allogeneic hematopoietic cell transplantation for sickle cell disease have improved outcomes, but there is limited analysis of healthcare utilization in this setting. We hypothesized that, compared to late transplantation, early transplantation (at age <10 years) improves outcomes and decreases healthcare utilization. We performed a retrospective study of children transplanted for sickle cell disease in the USA during 2000-2013 using two large databases. Univariate and Cox models were used to estimate associations of demographics, sickle cell disease severity, and transplant-related variables with mortality and chronic graft-versus-host disease, while Wilcoxon, Kruskal-Wallis, or linear trend tests were applied for the estimates of healthcare utilization. Among 161 patients with a 2-year overall survival rate of 90% (95% confidence interval [CI] 85-95%) mortality was significantly higher in those who underwent late transplantation versus early (hazard ratio (HR) 21, 95% CI 2.8-160.8, P=0.003) and unrelated compared to matched sibling donor transplantation (HR 5.9, 95% CI 1.7-20.2, P=0.005). Chronic graftversus host disease was significantly more frequent among those translanted late (HR 1.9, 95% CI 1.0-3.5, P=0.034) and those who received an unrelated graft (HR 2.5, 95% CI 1.2-5.4; P=0.017). Merged data for 176 patients showed that the median total adjusted transplant cost per patient was $467,747 (range: $344,029-$799,219). Healthcare utilization was lower among recipients of matched sibling donor grafts and those with low severity disease compared to those with other types of donor and disease severity types (P<0.001 and P=0.022, respectively); no association was demonstrated with late transplantation (P=0.775). Among patients with 2-year pre- and post-transplant data (n=41), early transplantation was associated with significant reductions in admissions (P<0.001), length of stay (P<0.001), and cost (P=0.008). Early transplant outcomes need to be studied prospectively in young children without severe disease and an available matched sibling to provide conclusive evidence for the superiority of this approach. Reduced post-transplant healthcare utilization inpatient care indicates that transplantation may provide a sustained decrease in healthcare costs over time.

39. Cognitive Function, Coping, and Depressive Symptoms in Children and Adolescents with Sickle Cell Disease.

Author(s): Prussien, Kemar V; DeBaun, Michael R; Yarboi, Janet; Bemis, Heather; McNally, Colleen; Williams, Ellen; Compas, Bruce E

Source: Journal of pediatric psychology; Nov 2017

Publication Type(s): Journal Article

Abstract: ObjectiveThe objective of this study was to investigate the association between cognitive functioning, coping, and depressive symptoms in children and adolescents with sickle cell disease (SCD).MethodForty-four children (M age = 9.30, SD = 3.08; 56.8% male) with SCD completed cognitive assessments measuring working memory (Wechsler Intelligence Scale for Children-Fourth Edition) and verbal comprehension (Wechsler Abbreviated Scale of Intelligence-Second Edition). Participants' primary caregivers completed questionnaires assessing their child's coping and depressive symptoms.ResultsVerbal comprehension was significantly positively associated with secondary control coping (cognitive reappraisal, acceptance, distraction), and both working memory and secondary control coping were negatively associated with depressive symptoms. In partial support of the primary study hypothesis, verbal comprehension had an indirect association with depressive symptoms through secondary control coping, whereas working memory had a direct association with depressive symptoms.ConclusionsThe results provide new evidence for the associations between cognitive function and coping, and the association of both of these processes with depressive symptoms in children with SCD. Findings provide potential implications for clinical practice, including interventions to improve children's cognitive functioning to attenuate depressive symptoms.

40. The emerging challenge of optimal blood pressure management and hypertensive syndromes in pregnant women with sickle cell disease: a review.

Author(s): Lari, Nabilah F; DeBaun, Michael R; Oppong, Samuel A

Source: Expert review of hematology; Nov 2017; vol. 10 (no. 11); p. 987-994

Publication Type(s): Journal Article Review

Abstract:INTRODUCTIONSickle cell disease (SCD) is one of the most common hemoglobinopathy, affecting a considerable proportion of black populations of African origin, Middle East and in the Indian sub-continent. Women with SCD are more likely to experience adverse pregnancy and delivery outcomes. Hypertensive diseases in pregnancy such as preeclampsia and eclampsia are more common in women with sickle cell disease. Areas covered: This review examined the influence of hypertension and SCD in pregnancy, and provides the preliminary evidence that the traditional systolic and diastolic blood pressure thresholds for hypertensive disorders such as pre-eclampsia and eclampsia may require reassessment in pregnant women with SCD. The causes of maternal and perinatal morbidity and mortality, hypertensive complications of pregnancy in women with and without sickle cell disease were reviewed. A MEDLINE database search using medical subject headings (MeSH) and keywords for articles regarding sickle cell disease, pregnancy and hypertension was performed. Expert commentary: Pregnancy in women with sickle cell disease is associated with high maternal and perinatal morbidity and mortality. Using the existing thresholds for diagnosis and treatment for hypertensive disease in pregnancy without adjustment to accommodate for the lower systolic and diastolic blood pressure in those with sickle cell disease may worsen an already poor maternal and perinatal outcome in this population.

41. Association of Guideline-Adherent Antibiotic Treatment With Readmission of Children With Sickle Cell Disease Hospitalized With Acute Chest Syndrome.

Author(s): Bundy, David G; Richardson, Troy E; Hall, Matthew; Raphael, Jean L; Brousseau, David C; Arnold, Staci D; Kalpatthi, Ram V; Ellison, Angela M; Oyeku, Suzette O; Shah, Samir S

Source: JAMA pediatrics; Nov 2017; vol. 171 (no. 11); p. 1090-1099

Publication Type(s): Multicenter Study Journal Article

Available at JAMA pediatrics - from EBSCO (MEDLINE Complete)

Abstract: ImportanceAcute chest syndrome (ACS) is a common, serious complication of sickle cell disease (SCD) and a leading cause of hospitalization and death in both children and adults with SCD. Little is known about the effectiveness of guideline-recommended antibiotic regimens for the care of children hospitalized with ACS.ObjectivesTo use a large, national database to describe patterns of antibiotic use for children with SCD hospitalized for ACS and to determine whether receipt of guideline-adherent antibiotics was associated with lower readmission rates.Design, Setting, and ParticipantsRetrospective cohort study including 14 480 hospitalizations in 7178 children (age 0-22 years) with a discharge diagnosis of SCD and either ACS or pneumonia. Information was obtained from 41 children's hospitals submitting data to the Pediatric Health Information System from January 1, 2010, to December 31, 2016.ExposuresNational Heart, Lung, and Blood Institute guideline-adherent (macrolide with parenteral cephalosporin) vs non-guideline-adherent antibiotic regimens.Main Outcomes and MeasuresAcute chest syndrome-related and all-cause 7- and 30-day readmissions.ResultsOf the 14 480 hospitalizations, 6562 (45.3%) were in girls; median (interquartile range) age was 9 (4-14) years. Guideline-adherent antibiotics were provided in 10 654 of 14 480 hospitalizations for ACS (73.6%). Hospitalizations were most likely to include guideline-adherent antibiotics for children aged 5 to 9 years (3230 of 4047 [79.8%]) and declined to the lowest level for children 19 to 22 years (697 of 1088 [64.1%]). Between-hospital variation in antibiotic regimens was wide, with use of guideline-adherent antibiotics ranging from 24% to 90%. Children treated with guideline-adherent antibiotics had lower 30-day ACS-related (odds ratio [OR], 0.71; 95% CI, 0.50-1.00) and all-cause (OR, 0.50; 95% CI, 0.39-0.64) readmission rates vs children who received other regimens (cephalosporin and macrolide vs neither drug class).Conclusions and RelevanceCurrent approaches to antibiotic treatment in children with ACS vary widely, but guideline-adherent therapy appears to result in fewer readmissions compared with non-guideline-adherent therapy. Efforts to increase the dissemination and implementation of SCD treatment guidelines are warranted as is comparative effectiveness research to strengthen the underlying evidence base.

42. CDC Grand Rounds: Improving the Lives of Persons with Sickle Cell Disease.

Author(s): Hulihan, Mary; Hassell, Kathryn L; Raphael, Jean L; Smith-Whitley, Kim; Thorpe, Phoebe

Source: MMWR. Morbidity and mortality weekly report; Nov 2017; vol. 66 (no. 46); p. 1269-1271

Publication Type(s): Journal Article

Available at MMWR. Morbidity and mortality weekly report - from EBSCO (Health Business FullTEXT Elite)

Available at MMWR. Morbidity and mortality weekly report - from EBSCO (CINAHL with Full Text)

Available at MMWR. Morbidity and mortality weekly report - from ProQuest (Hospital Premium Collection) - NHS Version

Available at MMWR. Morbidity and mortality weekly report - from EBSCO (MEDLINE Complete)

Available at MMWR. Morbidity and mortality weekly report - from nih.gov

Abstract: Approximately 100,000 Americans have sickle cell disease (SCD), a group of recessively inherited red blood cell disorders characterized by abnormal hemoglobin, called hemoglobin S or sickle hemoglobin, in the red blood cells. Persons with hemoglobin SS or hemoglobin Sß0 thalassemia, also known as sickle cell anemia (SCA), have the most severe form of SCD. Hemoglobin SC disease and hemoglobin Sß+ thalassemia are other common forms of SCD. Red blood cells that contain sickle hemoglobin are inflexible and can stick to vessel walls, causing a blockage that slows or stops blood flow. When this happens, oxygen cannot reach nearby tissues, leading to attacks of sudden, severe pain, called pain crises, which are the clinical hallmark of SCD. The red cell sickling and poor oxygen delivery can also cause damage to the brain, spleen, eyes, lungs, liver, and multiple other organs and organ systems. These chronic complications can lead to increased morbidity, early mortality, or both. Tremendous strides in treating and preventing the complications of SCD have extended life expectancy. Now, nearly 95% of persons born with SCD in the United States reach age 18 years (1); however, adults with the most severe forms of SCD have a life span that is 20-30 years shorter than that of persons without SCD (2).

43. Feasibility and Acceptability of Internet-delivered Cognitive Behavioral Therapy for Chronic Pain in Adolescents With Sickle Cell Disease and Their Parents.

Author(s): Palermo, Tonya M; Dudeney, Joanne; Santanelli, James P; Carletti, Alexie; Zempsky, William T

Source: Journal of pediatric hematology/oncology; Nov 2017

Publication Type(s): Journal Article

Abstract: Pain is a clinical hallmark of sickle cell disease (SCD), and is rarely optimally managed. Cognitive-behavioral therapy (CBT) for pain has been effectively delivered through the Internet in other pediatric populations. We tested feasibility and acceptability of an Internet-delivered CBT intervention in 25 adolescents with SCD (64% female, mean age=14.8 y) and their parents randomized to Internet CBT (n=15) or Internet Pain Education (n=10). Participants completed pretreatment/posttreatment measures. Eight dyads completed semistructured interviews to evaluate treatment acceptability. Feasibility indicators included recruitment and participation rates, engagement and adherence to intervention, and completion of outcome measures. In total, 87 referrals were received from 9 study sites; our recruitment rate was 60% from those families approached for screening. Among participants, high levels of initial intervention engagement (>90%), and adherence (>70%) were demonstrated. Most participants completed posttreatment outcome and diary measures (>75%). Retention at posttreatment was 80%. High treatment acceptability was reported in interviews. Our findings suggest that Internet-delivered CBT for SCD pain is feasible and acceptable to adolescents with SCD and their parents. Engagement and adherence were good. Next steps are to modify recruitment plans to enhance enrollment and determine efficacy of Internet CBT for SCD pain in a large multisite randomized controlled trial.

44. Are the risks of treatment to cure a child with severe sickle cell disease too high?

Author(s): de Montalembert, Mariane; Brousse, Valentine; Chakravorty, Subarna; Pagliuca, Antonio; Porter, John; Telfer, Paul; Vora, Ajay; Rees, David C

Source: BMJ (Clinical research ed.); Nov 2017; vol. 359 ; p. j5250

Publication Type(s): Journal Article

Available at BMJ (Clinical research ed.) - from BMJ Journals

Available at BMJ (Clinical research ed.) - from BMJ Journals - NHS

45. Pain Management for Sickle Cell Disease in the Pediatric Emergency Department: Medications and Hospitalization Trends.

Author(s): Cacciotti, Chantel; Vaiselbuh, Sarah; Romanos-Sirakis, Eleny

Source: Clinical pediatrics; Oct 2017; vol. 56 (no. 12); p. 1109-1114

Publication Type(s): Journal Article

Abstract: The majority of emergency department (ED) visits and hospitalizations for patients with sickle cell disease (SCD) are pain related. Adequate and timely pain management may improve quality of life and prevent worsening morbidities. We conducted a retrospective chart review of pediatric patients with SCD seen in the ED, selected by sickle cell-related ICD-9 codes. A total of 176 encounters were reviewed from 47 patients to record ED pain management and hospitalization trends. Mean time to pain medication administration was 63 minutes. Patients received combination (nonsteroidal anti-inflammatory drug [NSAID] + narcotic) pain medications for initial treatment at a minority of ED encounters (19%). A higher percentage of patients who received narcotics alone as initial treatment were hospitalized as compared with those who received combination treatment initially (P= 0.0085). Improved patient education regarding home pain management as well as standardized ED guidelines for assessment and treatment of sickle cell pain may result in superior and more consistent patient care.

46. Fertility challenges for women with sickle cell disease.

Author(s): Ghafuri, Djamila L; Stimpson, Sarah-Jo; Day, Melissa E; James, Andra; DeBaun, Michael R; Sharma, Deva

Source: Expert review of hematology; Oct 2017; vol. 10 (no. 10); p. 891-901

Publication Type(s): Meta-analysis Journal Article Review

Abstract:INTRODUCTIONSickle cell disease (SCD) represents one of the most common monogenic blood disorders worldwide, with an incidence of over 300,000 newborns affected per year. Reproductive challenges for men and women with SCD have been previously reviewed; however, evidence-based strategies to prevent and manage infertility and increase fecundity are lacking in women with SCD, which is one of the most important factors for quality of life. Areas covered: This review article summarizes the known risk factors for infertility, low fecundity, and premature menopause related to SCD. Expert commentary: Women with SCD have unique risk factors that may impact their ability to conceive, including chronic inflammation, oxidative stress, transfusion-related hemochromatosis, and ovarian sickling, causing ischemia and reperfusion injury to the ovary. Contraception is strongly recommended while on hydroxyurea therapy during reproductive years and discontinuing hydroxyurea for family planning and during pregnancy based on teratogenicity in animal studies. Hematopoietic stem cell transplantation (HSCT), the only curative therapy, sometimes involves conditioning regimens containing alkylating agents and total body irradiation that contribute to infertility and premature ovarian failure. Prior to HSCT or gene therapy, we strongly recommend referral to a reproductive endocrinologist to discuss fertility preservation and surrogacy options for all women with SCD.

47. Medical and economic implications of strategies to prevent alloimmunization in sickle cell disease.

Author(s): Gehrie, Eric A; Ness, Paul M; Bloch, Evan M; Kacker, Seema; Tobian, Aaron A R

Source: Transfusion; Sep 2017; vol. 57 (no. 9); p. 2267-2276

Publication Type(s): Journal Article Review

Available at Transfusion - from nih.gov

Abstract:BACKGROUNDThe pathogenesis of alloimmunization is not well understood, and initiatives that aim to reduce the incidence of alloimmunization are generally expensive and either ineffective or unproven. In this review, we summarize the current medical literature regarding alloimmunization in the sickle cell disease (SCD) population, with a special focus on the financial implications of different approaches to prevent alloimmunization.STUDY DESIGN AND METHODSA review of EMBASE and MEDLINE data from January 2006 through January 2016 was conducted to identify articles relating to complications of SCD. The search was specifically designed to capture articles that evaluated the costs of various strategies to prevent alloimmunization and its sequelae.RESULTSCurrently, there is no proven, inexpensive way to prevent alloimmunization among individuals with SCD. Serologic matching programs are not uniformly successful in preventing alloimmunization, particularly to Rh antigens, because of the high frequency of variant Rh alleles in the SCD population. A genotypic matching program could offer some cost savings compared to a serologic matching program, but the efficacy of gene matching for the prevention of alloimmunization is largely unproven, and large-scale implementation could be expensive.CONCLUSIONSFuture reductions in the costs associated with genotype matching could make a large-scale program economically feasible. Novel techniques to identify patients at highest risk for alloimmunization could improve the cost effectiveness of antigen matching programs. A clinical trial comparing the efficacy of serologic matching to genotype matching would be informative.

48. Applications of cardiac magnetic resonance imaging in sickle cell disease.

Author(s): Niss, Omar; Taylor, Michael D

Source: Blood cells, molecules & diseases; Sep 2017; vol. 67 ; p. 126-134

Publication Type(s): Journal Article

Abstract: Cardiac magnetic resonance imaging (CMR) has evolved from an effective research tool to a non-invasive clinical modality with versatile applications. The accuracy of volume measurements and functional assessment and the ability to identify unique myocardial tissue characteristics non-invasively are the primary advantages of CMR. The use of CMR in sickle cell disease (SCD) has been limited clinically to myocardial iron assessment. The use of other CMR applications to characterize the cardiac pathology in SCD is slowly emerging but remains limited to research level. In this review, we discuss some of the applications of CMR in studying cardiovascular diseases and its potential uses in SCD for research and clinical purposes.

49. Curative approaches for sickle cell disease: A review of allogeneic and autologous strategies.

Author(s): Bauer, Daniel E; Brendel, Christian; Fitzhugh, Courtney D

Source: Blood cells, molecules & diseases; Sep 2017; vol. 67 ; p. 155-168

Publication Type(s): Journal Article

Abstract: Despite sickle cell disease (SCD) first being reported >100years ago and molecularly characterized >50years ago, patients continue to experience severe morbidity and early mortality. Although there have been substantial clinical advances with immunizations, penicillin prophylaxis, hydroxyurea treatment, and transfusion therapy, the only cure that can be offered is hematopoietic stem cell transplantation (HSCT). In this work, we summarize the various allogeneic curative

approaches reported to date and discuss open and upcoming clinical research protocols. Then we consider gene therapy and gene editing strategies that may enable cure based on autologous HSCs.

50. Family Functioning, Medical Self-Management, and Health Outcomes Among School-Aged Children With Sickle Cell Disease: A Mediation Model.

Author(s): Psihogios, Alexandra M; Daniel, Lauren C; Tarazi, Reem; Smith-Whitley, Kim; Patterson, Chavis A; Barakat, Lamia P

Source: Journal of pediatric psychology; Sep 2017

Publication Type(s): Journal Article

Abstract: BackgroundInformed by the Pediatric Self-Management Model, the present study tested relationships between parent and family functioning, sickle cell disease (SCD) self-management, and health outcomes for children with SCD.Method83 children with SCD and a parent completed baseline data as part of a larger investigation of a family-based, problem-solving intervention for children with SCD (M age = 8.47). Youth and parents completed a measure of child health-related quality of life (HRQOL), and parents completed measures of family efficacy, parenting stress, and SCD self-management. SCD pain episodes and urgent health utilization information over the past year were obtained via medical chart review.ResultsSCD self-management mediated the relationship between parent-reported family efficacy and parent proxy HRQOL, as well as the relationship between parenting stress and child and parent proxy HRQOL. Mediation models were nonsignificant for outcomes beyond HRQOL, including SCD pain episodes and urgent health utilization.ConclusionFostering family efficacy and reducing parenting stress may be meaningful intervention targets for improving SCD self-management and child HRQOL among school-aged children. Although findings were consistent with the Pediatric Self-Management Model in terms of HRQOL, the model was not supported for pain episodes or urgent health utilization, highlighting the need for multi-method, longitudinal research on the SCD self-management behaviors that are linked to preventable health outcomes.

51. Pharmacotherapeutical strategies in the prevention of acute, vaso-occlusive pain in sickle cell disease: a systematic review.

Author(s): Sins, Joep W R; Mager, David J; Davis, Shyrin C A T; Biemond, Bart J; Fijnvandraat, Karin

Source: Blood advances; Aug 2017; vol. 1 (no. 19); p. 1598-1616

Publication Type(s): Journal Article Review

Available at Blood advances - from nih.gov

Abstract: Sickle-cell disease (SCD) is characterized by frequent and painful vaso-occlusive crises (VOCs). Various treatments have been evaluated over the years. However, a clear overview is lacking. The objective of this study was to systematically review all pharmacotherapeutical strategies in the prevention of VOCs beyond hydroxyurea. We performed a systematic literature search (MEDLINE, Embase, CENTRAL). Eligible studies were controlled clinical trials evaluating pharmacotherapeutical interventions targeting the reduction of VOCs in patients with SCD. Primary outcomes were the number or duration of SCD-related pain days, VOCs, or hospital admissions for VOCs. Secondary outcomes included time to first VOC or hospital admission for a VOC. A standardized data extraction sheet was used. The methodological quality of studies was assessed using Cochrane's risk-of-bias tool. A total of 36 studies were included in this review, covering 26 different prophylactic interventions. The most promising interventions for reducing the frequency of either VOCs or hospitalizations were the oral antioxidants l-glutamine and ω-3 fatty acids and the IV

antiadhesive agent crizanlizumab. Twenty-three studies did not show any beneficial effect of the intervention under investigation, and 6 studies were either too small or methodologically inadequate to draw conclusions. Because of the heterogeneity of interventions, no meta-analysis was performed. In conclusion, this review identified 3 promising pharmacotherapeutical strategies in the prevention of VOCs in SCD. Importantly, this study highlights the discrepancy between the significant burden of SCD worldwide and the low number of adequate trials performed. This review was registered at PROSPERO (CRD42015025250).

52. Patient Perspectives on Gene Transfer Therapy for Sickle Cell Disease.

Author(s): Strong, Heather; Mitchell, Monica J; Goldstein-Leever, Alana; Shook, Lisa; Malik, Punam; Crosby, Lori E

Source: Advances in therapy; Aug 2017; vol. 34 (no. 8); p. 2007-2021

Publication Type(s): Journal Article

Abstract:INTRODUCTIONSickle cell disease (SCD) is a chronic genetic disease with high morbidity and early mortality; it affects nearly 100,000 individuals in the USA. Bone marrow transplantation, the only curative treatment, is available to less than 20% of patients because of a number of access barriers. Gene transfer therapy (GTT) has been shown to be curative in animal models and is approved for use in humans for early-phase studies at a few centers. GTT would offer a more accessible treatment option available to all patients. It is important to understand patient perspectives on GTT to help ensure human clinical trial success.METHODSTwo focus groups were conducted with younger (18-30 years) and older (31 years and older) adults with SCD to obtain data on patient knowledge and beliefs about GTT. Data from these two focus groups was used to develop a GTT educational brochure. A third focus group was conducted to obtain participant feedback on acceptability and feasibility of education and the brochure.RESULTSMost adults, especially young adults, had little knowledge about GTT and expressed fear and uncertainty about the side effects of chemotherapy (e.g., hair loss, infertility), use of a human immunodeficiency virus (HIV)-derived viral vector, and potential for cancer risk. Participants wanted full transparency in educational materials, but advised researchers not to share the vector's relation to HIV because of cultural stigma and no HIV virus is used for the GTT vector.CONCLUSIONOlder adults had more desire to participate in human clinical GTT trials than younger participants. When recruiting for trials, researchers should develop GTT educational materials that address participant lack of trust in the healthcare system, cultural beliefs, fears related to side effects, and include visual illustrations. Use of such materials will provide adults with SCD the information they need to fully evaluate GTT.

53. Transcranial Doppler screening for stroke risk in children with sickle cell disease: a systematic review.

Author(s): Mazzucco, Sara; Diomedi, Marina; Qureshi, Amrana; Sainati, Laura; Padayachee, Soundrie T

Source: International journal of stroke : official journal of the International Stroke Society; Aug 2017; vol. 12 (no. 6); p. 580-588

Publication Type(s): Journal Article

Abstract: Background Sickle cell disease (SCD) is one of the most common causes of stroke in children worldwide. Based on the results of the Stroke Prevention Trial in Sickle Cell Anemia (STOP), annual transcranial Doppler ultrasound (TCD) screening for affected children is standard practice. However, the need for TCD surveillance programs could override the accuracy of the screening, affecting the correct stratification of stroke risk and subsequent clinical management of the target

population. Aims To shed light on this issue, a systematic review of the literature on TCD screening for children and adolescents with SCD was carried out (CRD42016050549), according to a list of clinically relevant questions, with a particular focus on screening practices in European countries. Quality of the evidence was rated using the grading of recommendations assessment, development and evaluation. Summary of review Thirty-three studies published in English or French were included (5 randomized controlled trials, 8 experimental non-randomized, and 20 observational studies). The quality of the retrieved evidence ranged between low and high, but was rated as moderate or high most of the times. TCD is effective as a screening tool for the primary prevention of stroke in SCD children. There is no high-quality evidence on the effectiveness of alternative screening methods, such as imaging-TCD with or without angle correction or magnetic resonance angiography. No evidence was found on effectiveness of the screening on children on hydroxyurea and with genotypes other than HbSS and HbS/β0. No European data were found on screening rates or adherence of screening practices to the STOP protocol. Conclusions High-quality studies on alternative screening methods that are currently used in real-world practice, and on screening applicability to specific subgroups of patients are urgently needed. Considering the low awareness of the disease in European countries and the lack of data on screening practices and adherence, clinicians need up-to-date guidelines for more uniform and evidence-based surveillance of children with SCD.

54. Perioperative considerations for patients with sickle cell disease: a narrative review.

Author(s): Khurmi, Narjeet; Gorlin, Andrew; Misra, Lopa

Source: Canadian journal of anaesthesia = Journal canadien d'anesthesie; Aug 2017; vol. 64 (no. 8); p. 860-869

Publication Type(s): Journal Article

Abstract:PURPOSEApproximately 200,000 individuals worldwide are born annually with sickle cell disease (SCD). Regions with the highest rates of SCD include Africa, the Mediterranean, and Asia, where its prevalence is estimated to be 2-6% of the population. An estimated 70,000-100,000 people in the United States have SCD. Due to enhanced newborn screening, a better understanding of this disease, and more aggressive therapy, many sickle cell patients survive into their adult years and present more frequently for surgery.SOURCEThe authors identified relevant medical literature by searching PubMed, MEDLINE®, EMBASE™, Scopus™, Web of Science, and Google Scholar databases for English language publications appearing from 1972-September 2016. Case reports, abstracts, review articles, and original research articles were reviewed-with particular focus on the pathophysiology and medical management of SCD and any anesthesia-related issues.PRINCIPAL FINDINGSPerioperative physicians should be familiar with the triggers of a sickle cell crisis and vaso-occlusive disease. Sickle cell disease affects various organ systems, including the central nervous, cardiovascular, pulmonary, genitourinary, and musculoskeletal systems. Preoperative assessment should focus on end-organ dysfunction. Controversy continues regarding if and when sickle cell patients should receive transfusions and which anesthetic technique (regional or general) confers any benefits. Timely, appropriate, and sufficient analgesia is critical, especially when patients experience a vaso-occlusive crisis, acute chest syndrome, or acute postoperative pain.CONCLUSIONEffective management of SCD patients in the perioperative setting requires familiarity with the epidemiology, pathophysiology, clinical manifestations, and treatment of SCD.

55. Acute and chronic hepatobiliary manifestations of sickle cell disease: A review.

Author(s): Shah, Rushikesh; Taborda, Cesar; Chawla, Saurabh

Source: World journal of gastrointestinal pathophysiology; Aug 2017; vol. 8 (no. 3); p. 108-116

Publication Type(s): Journal Article Review

Available at World journal of gastrointestinal pathophysiology - from Europe PubMed Central - Open Access

Abstract: Sickle cell disease (SCD) is a common hemoglobinopathy which can affect multiple organ systems in the body. Within the digestive tract, the hepatobiliary system is most commonly affected in SCD. The manifestations range from benign hyperbilirubinemia to overt liver failure, with the spectrum of acute clinical presentations often referred to as "sickle cell hepatopathy". This is an umbrella term referring to liver dysfunction and hyperbilirubinemia due to intrahepatic sickling process during SCD crisis leading to ischemia, sequestration and cholestasis. In this review, we detail the pathophysiology, clinical presentation and biochemical features of various acute and chronic hepatobiliary manifestations of SCD and present and evaluate existing evidence with regards to management of this disease process. We also discuss recent advances and controversies such as the role of liver transplantation in sickle cell hepatopathy and highlight important questions in this field which would require further research. Our aim with this review is to help increase the understanding, aid in early diagnosis and improve management of this important disease process.

56. Discontinuation of Folic Acid Supplementation in Young Patients With Sickle Cell Anemia.

Author(s): Nguyen, Giang-Kim T; Lewis, Angela; Goldener, Carol; Reed, Brenda; Dulman, Robin Yates; Yang, Elizabeth

Source: Journal of pediatric hematology/oncology; Aug 2017; vol. 39 (no. 6); p. 470-472

Publication Type(s): Journal Article

Abstract: Folic acid (FA) is commonly prescribed for patients with sickle cell anemia, but evidence for the efficacy of this practice is lacking. We stopped FA supplementation and measured red blood cell folate levels after discontinuation of FA in 72 patients with clinically severe forms of sickle cell disease. We compared hemoglobin and reticulocyte counts before and after FA discontinuation in 51 of those patients, the majority of whom were on hydroxyurea. No patients had red blood cell folate levels below normal and no significant difference in hemoglobin levels (P=0.18) or reticulocyte counts (P=0.37) was found before and after FA discontinuation.

57. The role of nutrition in the pathophysiology and management of sickle cell disease among children: A review of literature.

Author(s): Ohemeng, Agartha; Boadu, Isaac

Source: Critical reviews in food science and nutrition; Jul 2017 ; p. 1-7

Publication Type(s): Journal Article

Abstract: Sickle cell disease (SCD) is one of the common inherited blood disorders in humans and has been associated with decreased dietary intake which results in poor nutritional status and impaired growth. Nutrition is one of the most important but often forgotten aspect of care of patients with chronic disorders and there have been emerging concern in literature on increased nutritional needs of SCD patients. This paper sought to review the available literature on the roles of individual nutrients in the pathophysiology and management of SCD among children. Children with SCD have been shown to exhibit suboptimal status with respect to both macronutrients and micronutrients. Thus, nutrition could play an important role in the management of SCD. However, there is paucity of evidence coming from trials with large sample sizes to support the suggestion that supplementation with various nutrients that have been considered in this review will be helpful.

58. Adherence to hydroxyurea, health-related quality of life domains, and patients' perceptions of sickle cell disease and hydroxyurea: a cross-sectional study in adolescents and young adults.

Author(s): Badawy, Sherif M; Thompson, Alexis A; Lai, Jin-Shei; Penedo, Frank J; Rychlik, Karen; Liem, Robert I

Source: Health and quality of life outcomes; Jul 2017; vol. 15 (no. 1); p. 136

Publication Type(s): Journal Article

PubMedID: 28679417

Available at Health and quality of life outcomes - from BioMed Central

Available at Health and quality of life outcomes - from Europe PubMed Central - Open Access

Available at Health and quality of life outcomes - from EBSCO (MEDLINE Complete)

Available at Health and quality of life outcomes - from nih.gov

Abstract:BACKGROUNDSickle cell disease (SCD) patients have impaired domains of health-related quality of life (HRQOL). Hydroxyurea is safe and efficacious in SCD; however, adherence is suboptimal, and patients' perceptions are poorly understood amongst adolescents and young adults (AYA). Study objectives were to: (1) examine patients' perceptions of SCD and hydroxyurea; and (2) explore the relationship of their perceptions to clinical characteristics, HRQOL domains and hydroxyurea adherence.METHODSThirty-four SCD patients on hydroxyurea (≥6 months) participated in a single-institution study. Study measures included Brief-Illness Perceptions Questionnaire, ©Modified Morisky Adherence Scale 8-items, and Patient Reported Outcomes Measurement Information System (PROMIS®). We assessed the relationship of patients' perceptions to hydroxyurea adherence using Wilcoxon rank-sum test, the number of hospitalizations using Kruskal-Wallis test, and the number of ED visits, adherence level, HRQOL domain scores using Spearman's rho correlations. We conducted a sub-analysis in HbSS patients to evaluate the relationship of patients' perceptions to laboratory markers of hydroxyurea adherence.RESULTSParticipants were 59% male and 91% Black, and had a median age of 13.5 (range 12-18) years. Participants with ≥4 hospitalizations over 1-year prior (using electronic medical chart review) reported more negative perceptions of SCD-related symptoms and emotional response, and perceived hydroxyurea as less beneficial; all p-values ≤0.01. Most participants (74%) reported low hydroxyurea adherence. Participants with higher hydroxyurea adherence perceived more hydroxyurea benefits ($r_s = 0.44$, $p < 0.01$) and had better emotional response to SCD ($r_s = -0.44$, $p = 0.01$). In a sub-analysis of HbSS patients, perceived benefits of hydroxyurea positively correlated with HbF ($r_s = 0.37$, $p = 0.05$) and MCV values ($r_s = 0.35$, $p = 0.05$). Participants with more negative perceptions of SCD-related consequences, concerns, and emotional response, and fewer perceived hydroxyurea benefits reported worse fatigue ($r_s = 0.68$; $r_s = 0.44$; $r_s = 0.74$; $r_s = -0.60$), pain ($r_s = 0.56$; $r_s = 0.54$; $r_s = 0.63$; $r_s = -0.39$), anxiety ($r_s = 0.55$; $r_s = 0.58$; $r_s = 0.56$; $r_s = -0.47$), and depression ($r_s = 0.64$; $r_s = 0.49$; $r_s = 0.70$; $r_s = -0.62$), respectively, all p-values <0.05.CONCLUSIONSDynamics influencing hydroxyurea adherence are multifactorial, and understanding patients' perceptions is critical to overcoming adherence barriers. Patients' favorable perceptions correlated with greater adherence and better HRQOL domain scores. Prospective evaluation of patients' perceptions of SCD and hydroxyurea in relation adherence, HRQOL domains and clinical outcomes is warranted.

59. A systematic review of the literature for severity predictors in children with sickle cell anemia.

Author(s): Meier, Emily Riehm; Fasano, Ross M; Levett, Paul R

Source: Blood cells, molecules & diseases; Jun 2017; vol. 65 ; p. 86-94

Publication Type(s): Journal Article

Abstract: All patients with HbSS (SCA) share the same genetic mutation but the clinical phenotype is variable and difficult to predict early in life. A reliable severity predictor would be invaluable toward directing therapeutic decisions in those patients at highest risk of SCA complications. A search of PubMed, Cochrane Clinical Trials Register, and Scopus was performed to determine which SCA severity predictors have been validated in pediatric patients. The full text of 94 of the 590 references identified was reviewed based on the title/abstract. Fifty-four articles were included in the analysis. Alpha globin gene number was the most commonly studied severity predictor, followed by fetal hemoglobin (HbF) and reticulocyte count. Alpha thalassemia trait was protective against overt stroke and abnormal transcranial Doppler (TCD) in all but one study, but not frequency of painful crisis or silent cerebral infarct. Two thirds of the HbF studies reported beneficial effects with increasing HbF levels; however, increased HbF levels were not associated with lower hospitalization or stroke rates in others. The ability to predict SCA complications was mixed for all variables, except TCD and absolute reticulocyte count. More reliable predictors are urgently needed to guide therapeutic decisions in children with SCA.

60. Novel Metrics in the Longitudinal Evaluation of Pain Data in Sickle Cell Disease.

Author(s): Bakshi, Nitya; Smith, Meagan E; Ross, Diana; Krishnamurti, Lakshmanan

Source: The Clinical journal of pain; Jun 2017; vol. 33 (no. 6); p. 517-527

Publication Type(s): Journal Article

Abstract:BACKGROUNDAvailable modalities for the longitudinal capture and analysis of pain intensity in patients with sickle cell disease (SCD) limit our ability to study intraindividual and interindividual variation in pain and the factors influencing the transition from acute to chronic pain in patients with SCD.OBJECTIVESThe objectives of this study were to determine the feasibility of electronic capture of longitudinal outpatient pain intensity data and to test the applicability of novel metrics in the study of intraindividual and interindividual variation in pain in patients with SCD.MATERIALS AND METHODSTwenty SCD patients aged 13 to 21 submitted 2045 diary days of pain intensity data over 229 days using a web-based electronic pain diary or through text message.RESULTSParticipants reported pain (11-point Numerical Rating Score >0) on 1559 diary days (76.2%) suggesting a significant outpatient pain burden. In addition to mean maximum daily pain (MMDP), using maximum daily pain (MDP) scores, we calculated the ninetieth percentile (p90) of MDP, proportion of pain-free days (PPFD), Standard Deviation (SD) of MDP and coefficient of variation (CV) of MDP. Although p50 of MDP and p90 of MDP correlated positively with MMDP, PPFD correlated negatively with MMDP and both MMDP and PPFD correlated poorly with the SD of MDP. Examination of graphic representation of pain trends demonstrated how patients with similar MMDP had varying p90, PPFD, SD/coefficient of variation, and ultimately burden of pain over time. Missing data rates were lowest in the first 30 days of reporting and increased over time. Study participants reported a positive experience with momentary pain reporting and improved communication with health care providers regarding pain.CONCLUSIONSThe longitudinal collection of pain data with the inclusion of hospital data during periods of hospitalization is feasible and acceptable in patients with SCD over periods of 30 to 60 days. Long-term collection of pain diary data, while informative, is associated with higher rates of missing data. Novel metrics of pain have the potential to better describe intraindividual and interindividual variation in pain, inform studies of the transition from acute to chronic pain as well as contribute patient-reported end points of pain for interventional clinical trials of pain in SCD.

61. Therapeutic strategies in Sickle Cell Anemia: The past present and future.

Author(s): Fernandes, Queenie

Source: Life sciences; Jun 2017; vol. 178 ; p. 100-108

Publication Type(s): Journal Article Review

Abstract: Sickle Cell Anemia (SCA) was one of the first hemoglobinopathies to be discovered. It is distinguished by the mutation-induced expression of a sickle cell variant of hemoglobin (HbS) that triggers erythrocytes to take a characteristic sickled conformation. The complex physiopathology of the disease and its associated clinical complications has initiated multi-disciplinary research within its field. This review attempts to lay emphasis on the evolution, current standpoint and future scope of therapeutic strategies in SCA.

62. Clinical 'pearls' of maternal critical care Part 2: sickle-cell disease in pregnancy.

Author(s): Patil, Vinod; Ratnayake, Gamunu; Fastovets, Galina

Source: Current opinion in anaesthesiology; Jun 2017; vol. 30 (no. 3); p. 326-334

Publication Type(s): Journal Article

Abstract:PURPOSE OF REVIEWThe current review outlines the challenges in managing pregnant women with sickle-cell anemia, who are at risk of becoming critically ill during pregnancy.RECENT FINDINGSSickle obstetric patients pose unique challenges to the anesthetist and intensivist. We discuss the role of prophylactic transfusions for specific indications like acute anemia and twin pregnancies. The management and prevention of vaso-occlusive crises and chest crisis are also outlined. The role of the multidisciplinary team cannot be overstated.Massive obstetric hemorrhage in this population is difficult, and unique considerations such as cell-saver technology and tranexamic acid usage are discussed. Secondary complications such as pulmonary hypertension and stroke are also considered, with a summary of the latest treatment guidelines.SUMMARYThis is a challenging cohort of pregnant patients who have a significantly increased morbidity and mortality. This review aims to aid management of these patients on the labor ward for both obstetric anesthetists and intensivists.

63. How we manage iron overload in sickle cell patients.

Author(s): Coates, Thomas D; Wood, John C

Source: British journal of haematology; Jun 2017; vol. 177 (no. 5); p. 703-716

Publication Type(s): Journal Article Review

Abstract: Blood transfusion plays a prominent role in the management of patients with sickle cell disease (SCD), but causes significant iron overload. As transfusions are used to treat the severe complications of SCD, it remains difficult to distinguish whether organ damage is a consequence of iron overload or is due to the complications treated by transfusion. Better management has resulted in increased survival, but prolonged exposure to iron puts SCD patients at greater risk for iron-related complications that should be treated. The success of chelation therapy is dominated by patient adherence to prescribed treatment; thus, adjustment of drug regimens to increase adherence to treatment is critical. This review will discuss the current biology of iron homeostasis in patients with SCD and how this informs our clinical approach to treatment. We will present the clinical approach to treatment of iron overload at our centre using serial assessment of organ iron by magnetic resonance imaging.

64. AAPT Diagnostic Criteria for Chronic Sickle Cell Disease Pain.

Author(s): Dampier, Carlton; Palermo, Tonya M; Darbari, Deepika S; Hassell, Kathryn; Smith, Wally; Zempsky, William

Source: The journal of pain : official journal of the American Pain Society; May 2017; vol. 18 (no. 5); p. 490-498

Publication Type(s): Journal Article

Abstract: Pain in sickle cell disease (SCD) is associated with increased morbidity, mortality, and high health care costs. Although episodic acute pain is the hallmark of this disorder, there is an increasing awareness that chronic pain is part of the pain experience of many older adolescents and adults. A common set of criteria for classifying chronic pain associated with SCD would enhance SCD pain research efforts in epidemiology, pain mechanisms, and clinical trials of pain management interventions, and ultimately improve clinical assessment and management. As part of the collaborative effort between the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks public-private partnership with the U.S. Food and Drug Administration and the American Pain Society, the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks-American Pain Society Pain Taxonomy initiative developed the outline of an optimal diagnostic system for chronic pain conditions. Subsequently, a working group of experts in SCD pain was convened to generate core diagnostic criteria for chronic pain associated with SCD. The working group synthesized available literature to provide evidence for the dimensions of this disease-specific pain taxonomy. A single pain condition labeled chronic SCD pain was derived with 3 modifiers reflecting different clinical features. Future systematic research is needed to evaluate the feasibility, validity, and reliability of these criteria.PERSPECTIVEAn evidence-based classification system for chronic SCD pain was constructed for the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks-American Pain Society Pain Taxonomy initiative. Applying this taxonomy may improve assessment and management of SCD pain and accelerate research on epidemiology, mechanisms, and treatments for chronic SCD pain.

65. Oxidative pathways in the sickle cell and beyond.

Author(s): Alayash, Abdu I

Source: Blood cells, molecules & diseases; May 2017

Publication Type(s): Journal Article Review

Abstract: Polymerization of deoxy sickle cell hemoglobin (HbS) is well recognized as the primary event that triggers the classic cycles of sickling/unsickling of patients red blood cells (RBCs). RBCs are also subjected to continuous endogenous and exogenous oxidative onslaughts resulting in hemolytic rate increases which contribute to the evolution of vasculopathies associated with this disease. Compared to steady-state conditions, the occurrences of vaso-occlusive crises increase the levels of both RBC-derived microparticles as well as extracellular Hb in circulation. Common byproduct resulting from free Hb oxidation and from Hb-laden microparticles is heme (now recognized as damage associated molecular pattern (DAMP) molecule) which has been shown to initiate inflammatory responses. This review provides new insights into the interplay between microparticles, free Hb and heme focusing on Hb's pseudoperoxidative activity that drives RBC's cytosolic, membrane changes as well as oxidative toxicity towards the vascular system. Emerging antioxidative strategies that include the use of protein and heme scavengers in controlling Hb oxidative pathways are discussed.

66. Opioid prescription practices at discharge and 30-day returns in children with sickle cell disease and pain.

Author(s): Okorji, Leslie M; Muntz, Devin S; Liem, Robert I

Source: Pediatric blood & cancer; May 2017; vol. 64 (no. 5)

Publication Type(s): Journal Article

Abstract:BACKGROUNDAcute pain episodes in children with sickle cell disease (SCD) represent a leading cause of readmissions. We examined prescription practices at the time of discharge in children with SCD presenting with acute pain to determine their impact on 30-day emergency department (ED) revisits and readmissions.METHODSIn this single-institution, 5-year retrospective study, we reviewed 290 encounters of patients with SCD aged 7-21 years hospitalized or discharged from the ED with acute pain. We reviewed demographic, treatment and discharge data, and 30-day returns, defined as ED revisits and readmissions within 30 days of discharge. Bivariate and multivariable analyses were performed to evaluate the association between discharge prescription practices and 30-day returns.RESULTSCompared to hospitalizations, treat-and-release ED visits for acute pain were associated with a higher incidence of 30-day returns (OR = 2.7 [95% CI: 1.5-4.8], P < 0.01). We found no association between prescribed opioid frequency (scheduled vs. as-needed) and 30-day returns (OR = 1.12 [95% CI: 0.62-2.02], P = 0.70). By multivariable logistic regression, the prescription of nonsteroidal anti-inflammatory drugs (NSAIDs) only, without opioids, after treat-and-release ED visits was independently associated with a higher frequency of 30-day ED revisits (OR = 6.9 [95% CI: 1.3-37.3], P = 0.03) but not readmissions.CONCLUSIONVariability exists in opioid prescription practices after discharge in children with SCD and pain episodes. Prescription of NSAIDs only, without opioids, was an independent predictor of higher 30-day ED revisits. Formalized studies to better understand factors that influence returns, including outpatient opioid management, are warranted in this population.

67. Risk factors for mortality in adult patients with sickle cell disease: a meta-analysis of studies in North America and Europe.

Author(s): Maitra, Poulami; Caughey, Melissa; Robinson, Laura; Desai, Payal C; Jones, Susan; Nouraie, Mehdi; Gladwin, Mark T; Hinderliter, Alan; Cai, Jianwen; Ataga, Kenneth I

Source: Haematologica; Apr 2017; vol. 102 (no. 4); p. 626-636

Publication Type(s): Research Support, N.i.h., Extramural Meta-analysis Journal Article

Available at Haematologica - from HighWire - Free Full Text

Available at Haematologica - from Europe PubMed Central - Open Access

Available at Haematologica - from EBSCO (MEDLINE Complete)

Available at Haematologica - from nih.gov

Abstract: Although recent studies show an improved survival of children with sickle cell disease in the US and Europe, for adult patients mortality remains high. This study was conducted to evaluate the factors associated with mortality in adult patients following the approval of hydroxyurea. We first evaluated the association between selected variables and mortality at an academic center (University of North Carolina). Data sources were then searched for publications from 1998 to June 2016, with meta-analysis of eligible studies conducted in North America and Europe to evaluate the associations of selected variables with mortality in adult patients. Nine studies, combined with the UNC cohort (total n=3257 patients) met the eligibility criteria. Mortality was significantly associated with age (per 10-year increase in age) [7 studies, 2306 participants; hazard ratio (HR): 1.28; 95% confidence interval (CI): 1.10-1.50], tricuspid regurgitant jet velocity 2.5 m/s or more (5 studies, 1577 participants; HR: 3.03; 95%CI: 2.0-4.60), reticulocyte count (3 studies, 1050 participants; HR: 1.05;

95%CI: 1.01-1.10), log(N-terminal-pro-brain natriuretic peptide) (3 studies, 800 participants; HR: 1.68; 95%CI: 1.48-1.90), and fetal hemoglobin (7 studies, 2477 participants; HR: 0.97; 95%CI: 0.94-1.0). This study identifies variables associated with mortality in adult patients with sickle cell disease in the hydroxyurea era.

68. The quality of information about sickle cell disease on the Internet for youth.

Author(s): Breakey, Vicky R; Harris, Lauren; Davis, Omar; Agarwal, Arnav; Ouellette, Carley; Akinnawo, Elizabeth; Stinson, Jennifer

Source: Pediatric blood & cancer; Apr 2017; vol. 64 (no. 4)

Publication Type(s): Journal Article

Abstract:BACKGROUNDAdolescence is a vulnerable time for teens with sickle cell disease (SCD). Although there is evidence to support the use of web-based education to promote self-management skills in patients with chronic illnesses, the quality of SCD-related information on the Internet has not been assessed.PROCEDUREA website review was conducted to appraise the quality, content, accuracy, readability, and desirability of online information for the adolescents with SCD. Relevant keywords were searched on the most popular search engines. Websites meeting predetermined criteria were reviewed. The quality of information was appraised using the validated DISCERN tool. Two physicians independently rated website completeness and accuracy. Readability of the sites was documented using the simple measure of gobbledygook (SMOG) scores and the Flesch Reading Ease (FRE). The website features considered desirable by youth were tracked.RESULTSSearch results yielded >600 websites with 25 unique hits meeting criteria. The overall quality of the information was "fair" and the average DISCERN rating score was 50.1 (±9.3, range 31.0-67.5). Only 12 of 25 (48%) websites had scores >50. The average completeness score was 20 of 29 (±5, range 12-27). No errors were identified. The mean SMOG score was 13.04 (±2.80, range 10.21-22.85) and the mean FRE score was 46.05 (±11.47; range 17.50-66.10), suggesting that the material was written well beyond the acceptable reading level for patient education. The websites were text-heavy and lacked the features that appeal to youth (chat, games, videos, etc.).CONCLUSIONGiven the paucity of high-quality health information available for the teens with SCD, it is essential that additional online resources be developed.

69. Associations between environmental factors and hospital admissions for sickle cell disease.

Author(s): Piel, Frédéric B; Tewari, Sanjay; Brousse, Valentine; Analitis, Antonis; Font, Anna; Menzel, Stephan; Chakravorty, Subarna; Thein, Swee Lay; Inusa, Baba; Telfer, Paul; de Montalembert, Mariane; Fuller, Gary W; Katsouyanni, Klea; Rees, David C

Source: Haematologica; Apr 2017; vol. 102 (no. 4); p. 666-675

Publication Type(s): Journal Article

Available at Haematologica - from HighWire - Free Full Text

Available at Haematologica - from Europe PubMed Central - Open Access

Available at Haematologica - from EBSCO (MEDLINE Complete)

Abstract: Sickle cell disease is an increasing global health burden. This inherited disease is characterized by a remarkable phenotypic heterogeneity, which can only partly be explained by genetic factors. Environmental factors are likely to play an important role but studies of their impact on disease severity are limited and their results are often inconsistent. This study investigated associations between a range of environmental factors and hospital admissions of young patients with sickle cell disease in London and in Paris between 2008 and 2012. Specific analyses were

conducted for subgroups of patients with different genotypes and for the main reasons for admissions. Generalized additive models and distributed lag non-linear models were used to assess the magnitude of the associations and to calculate relative risks. Some environmental factors significantly influence the numbers of hospital admissions of children with sickle cell disease, although the associations identified are complicated. Our study suggests that meteorological factors are more likely to be associated with hospital admissions for sickle cell disease than air pollutants. It confirms previous reports of risks associated with wind speed (risk ratio: 1.06/standard deviation; 95% confidence interval: 1.00-1.12) and also with rainfall (1.06/standard deviation; 95% confidence interval: 1.01-1.12). Maximum atmospheric pressure was found to be a protective factor (0.93/standard deviation; 95% confidence interval: 0.88-0.99). Weak or no associations were found with temperature. Divergent associations were identified for different genotypes or reasons for admissions, which could partly explain the lack of consistency in earlier studies. Advice to patients with sickle cell disease usually includes avoiding a range of environmental conditions that are believed to trigger acute complications, including extreme temperatures and high altitudes. Scientific evidence to support such advice is limited and sometimes confusing. This study shows that environmental factors do explain some of the variations in rates of admission to hospital with acute symptoms in sickle cell disease, but the associations are complex, and likely to be specific to different environments and the individual's exposure to them. Furthermore, this study highlights the need for prospective studies with large numbers of patients and standardized protocols across Europe.

70. Factors influencing utilization of hospital services by adult sickle cell disease patients: a systematic review.

Author(s): Benenson, Irina; Jadotte, Yuri; Echevarria, Mercedes

Source: JBI database of systematic reviews and implementation reports; Mar 2017; vol. 15 (no. 3); p. 765-808

Publication Type(s): Journal Article

Abstract:BACKGROUNDPainful vaso-occlusive crisis is a hallmark of sickle cell disease (SCD) that commonly results in utilization of hospital services. Recurrent use of hospital services by SCD patients is associated with high healthcare costs and adverse clinical outcomes. Understanding the factors influencing the pattern of utilization is a first step in improving medical care of this patient population while reducing healthcare expenditures.OBJECTIVESThe primary objective of this systematic review was to determine what modifiable and non-modifiable factors influence utilization of hospital services by adult SCD patients.INCLUSION CRITERIA TYPES OF PARTICIPANTSAdult SCD patients of both sexes who utilized hospital services for acute or emergency care.TYPES OF FACTORS/EXPOSURENon-modifiable and modifiable factors influencing utilization of hospital services.TYPES OF STUDIESProspective and retrospective cohort studies, case-control and analytical cross-sectional studies.OUTCOMESThe primary outcome of interest was high utilization of hospital services by adult SCD patients based on non-modifiable and modifiable factors measured as an odds ratio (analytical outcome). The secondary outcome was the prevalence of non-modifiable and modifiable factors among SCD patients who utilized hospital services measured as an event rate (descriptive outcome).SEARCH STRATEGYA comprehensive multi-step search was undertaken to find both published and unpublished studies. Only studies published in the English language were included. The search was not limited by year of publication.METHODOLOGICAL QUALITYRetrieved papers were assessed for methodological quality using standardized critical appraisal instruments from the Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument.DATA EXTRACTIONData were extracted using a researcher-developed tool.DATA SYNTHESISIncluded studies were combined in a statistical meta-analysis. The meta-analysis was based on a random

effect model. For studies that did not allow statistical pooling, the findings have been presented in a narrative form.RESULTSFourteen studies were included in this review. The analysis demonstrated that male patients accounted for 40.8% (95% confidence interval [CI] 0.370-0.447) of all utilizing patients. Sickle cell disease patients who were publically insured accounted for 76.5% (95% CI 0.632-0.861) of all patients who had hospital encounters. Patients aged 25-35 years had the highest rate of utilization, and the rate of utilization declined in patients older than 50 years. High utilizing patients had more diagnoses of acute chest syndrome and sepsis than patients who were moderate or low utilizers.CONCLUSIONThe majority of SCD patients who utilized hospital services were women, young people and publically insured individuals. Patients with particularly high level of utilization had more frequent diagnoses of acute chest syndrome and sepsis.

71. Sickle Cell Disease: A Brief Update.

Author(s): Azar, Sharl; Wong, Trisha E

Source: The Medical clinics of North America; Mar 2017; vol. 101 (no. 2); p. 375-393

Publication Type(s): Journal Article Review

Abstract: Sickle cell disease (SCD) is an inherited monogenic disease characterized by misshapen red blood cells that causes vaso-occlusive disease, vasculopathy, and systemic inflammation. Approximately 300,000 infants are born per year with SCD globally. Acute, chronic, and acute-on-chronic complications contribute to end-organ damage and adversely affect quantity and quality of life. Hematopoietic stem cell transplantation is the only cure available today, but is not feasible for the vast majority of people suffering from SCD. Fortunately, new therapies are in late clinical trials and more are in the pipeline, offering hope for this unfortunate disease, which has increasing global burden.

72. Transfusion Therapy in Children With Sickle Cell Disease.

Author(s): Inati, Adlette; Mansour, Anthony G; Sabbouh, Toni; Amhez, Ghid; Hachem, Ahmad; Abbas, Hussein A

Source: Journal of pediatric hematology/oncology; Mar 2017; vol. 39 (no. 2); p. 126-132

Publication Type(s): Journal Article Review

Abstract: Hydroxyurea, blood transfusions, and hematopoietic stem cell transplantation represent the 3 disease-modifying therapies in children with sickle cell disease (SCD). Blood transfusions play an increasingly important role in both prevention and management of SCD complications in this age group. This review will focus on the indications of blood transfusion in children with SCD and modalities of its administration. It will also highlight the complications of this life-saving therapy and ways of optimizing transfusion to minimize its associated risks.

73. A Prospective Emergency Department Quality Improvement Project to Improve the Treatment of Vaso-Occlusive Crisis in Sickle Cell Disease: Lessons Learned.

Author(s): Tanabe, Paula; Freiermuth, Caroline E; Cline, David M; Silva, Susan

Source: Joint Commission journal on quality and patient safety; Mar 2017; vol. 43 (no. 3); p. 116-126

Publication Type(s): Journal Article

Abstract:BACKGROUNDGuidelines recommend rapid, aggressive management of vaso-occlusive crisis (VOC) for patients with sickle cell disease (SCD). A large prospective research and quality

improvement (QI) project was conducted to measure changes in clinical outcomes in two EDs-academic medical centers with emergency medicine residency programs and Level 1 trauma centers-during a 2.5-year time period (October 2011-March 2014).METHODSA QI team used a Plan-Do-Study-Act approach to modify and implement changes to opioid analgesic protocols for the emergency department (ED) treatment of VOC. Data were collected quarterly; the team reviewed the results and made modifications to improve outcomes. A structured health record review was conducted to assess clinical outcomes (10 records/quarter/site). Patient interviews were conducted to measure satisfaction with pain management. Outcomes were compared before (T1) and after (T2) implementation of an electronic health record (EHR).RESULTSOne hundred ninety-six ED health records (118 unique patients, mean age = 32 [standard deviation, 11], 51% male) were analyzed. Before implementation, trends in decreasing time to initial analgesic administration were noted. There was a statistically significant increase in arrival to administration of first analgesic time between T1 and T2 at Site 1 but not at Site 2. Neither site showed significant changes in time between the administration of the first and second opioid doses, total opioid dose administered, or patient satisfaction.CONCLUSIONWhile QI efforts initially shortened door-to-analgesic times, these gains were not sustained. The lessons learned can help other EDs improve the timely delivery of analgesics to patients with SCD.

74. Developing new pharmacotherapeutic approaches to treating sickle-cell disease.

Author(s): Telen, Marilyn J

Source: ISBT science series; Feb 2017; vol. 12 (no. 1); p. 239-247

Publication Type(s): Journal Article

Abstract: Survival for patients with SCD has been prolonged by improvements in supportive care, including vaccinations, antibiotic prophylaxis, and overall medical management, including tra nsfusion. However, there remains only one approved, partially effective drug for sickle cell disease-hydroxyurea (hydroxycarbamide). The world desperately needs better ways of both treating and preventing the recurrent painful vaso-occlusive episodes pathognomonic of sickle cell disease as well as the end-organ damage that still leads inexorably to severely shortened life expectancies throughout the world. Based on accumulating knowledge about how the abnormal red blood cells of sickle cell disease cause the double scourge of acute painful episodes and progressive end-organ damage, both pharmaceutical enterprises and individual investigators are now pursuing multiple new avenues for treating sickle cell disease. As a result, many compounds are in active development, both in preclinical models as well as in phase I, II, and III clinical trials. These agents target many pathophysiologic processes thought to be critical in sickle cell disease, including the chemical and physical behavior of haemoglobin S, cell adhesion, coagulation pathways, platelet activation, inflammatory pathways, and upregulation of haemoglobin F expression. In addition, recent explorations of the genetic variations that predispose to certain types of sickle cell disease-related tissue injury, such as stroke or nephropathy, are expected to lead to identification of drugs targeting the pathways uncovered by such work. Thus, the next five to ten years holds a promise of new treatments for sickle cell disease.

75. Knowledge insufficient: the management of haemoglobin SC disease.

Author(s): Pecker, Lydia H; Schaefer, Beverly A; Luchtman-Jones, Lori

Source: British journal of haematology; Feb 2017; vol. 176 (no. 4); p. 515-526

Publication Type(s): Journal Article Review

Available at British journal of haematology - from Wiley Online Library Free Content - NHS

Abstract: Although haemoglobin SC (HbSC) accounts for 30% of sickle cell disease (SCD) in the United States and United Kingdom, evidence-based guidelines for genotype specific management are lacking. The unique pathology of HbSC disease is complex, characterized by erythrocyte dehydration, intracellular sickling and increased blood viscosity. The evaluation and treatment of patients with HbSC is largely inferred from studies of SCD consisting mostly of haemoglobin SS (HbSS) patients. These studies are underpowered to allow definitive conclusions about HbSC. We review the pathophysiology of HbSC disease, including known and potential differences between HbSS and HbSC, and highlight knowledge gaps in HbSC disease management. Clinical and translational research is needed to develop targeted treatments and to validate management recommendations for efficacy, safety and impact on quality of life for people with HbSC.

76. Kinetic assay shows that increasing red cell volume could be a treatment for sickle cell disease.

Author(s): Li, Quan; Henry, Eric R; Hofrichter, James; Smith, Jeffrey F; Cellmer, Troy; Dunkelberger, Emily B; Metaferia, Belhu B; Jones-Straehle, Stacy; Boutom, Sarah; Christoph, Garrott W; Wakefield, Terri H; Link, Mary E; Staton, Dwayne; Vass, Erica R; Miller, Jeffery L; Hsieh, Matthew M; Tisdale, John F; Eaton, William A

Source: Proceedings of the National Academy of Sciences of the United States of America; Jan 2017; vol. 114 (no. 5); p. E689

Publication Type(s): Journal Article

Abstract: Although it has been known for more than 60 years that the cause of sickle cell disease is polymerization of a hemoglobin mutant, hydroxyurea is the only drug approved for treatment by the US Food and Drug Administration. This drug, however, is only partially successful, and the discovery of additional drugs that inhibit fiber formation has been hampered by the lack of a sensitive and quantitative cellular assay. Here, we describe such a method in a 96-well plate format that is based on laser-induced polymerization in sickle trait cells and robust, automated image analysis to detect the precise time at which fibers distort ("sickle") the cells. With this kinetic method, we show that small increases in cell volume to reduce the hemoglobin concentration can result in therapeutic increases in the delay time prior to fiber formation. We also show that, of the two drugs (AES103 and GBT440) in clinical trials that inhibit polymerization by increasing oxygen affinity, one of them (GBT440) also inhibits sickling in the absence of oxygen by two additional mechanisms.

77. Sickle cell disease in the older adult.

Author(s): Thein, Mya S; Igbineweka, Norris E; Thein, Swee Lay

Source: Pathology; Jan 2017; vol. 49 (no. 1); p. 1-9

Publication Type(s): Journal Article Review

Abstract: Sickle cell disease (SCD) is an inherited haemoglobin disorder, associated with recurrent painful episodes, ongoing haemolytic anaemia and progressive multi-organ damage. Until the early 1990s, survival beyond the fourth decade for a patient with SCD was considered unusual and prompted case reports. Nowadays, in countries with developed health care systems, more than 90

percent of newborns with SCD survive into adulthood. Nevertheless, their life expectancy is still shortened by more than two decades compared to the general population. With an increasing life expectancy, SCD has now evolved into a debilitating disorder with substantial morbidity resulting from ongoing sickle cell vasculopathy and multi-organ damage. Limited data on health care issues of older adults with SCD poses multiple challenges to patients, their families and health care providers. In this review, we will address and discuss acute and chronic complications of SCD with a special focus on the older adult.

78. Biomechanics and biorheology of red blood cells in sickle cell anemia.

Author(s): Li, Xuejin; Dao, Ming; Lykotrafitis, George; Karniadakis, George Em

Source: Journal of biomechanics; Jan 2017; vol. 50 ; p. 34-41

Publication Type(s): Research Support, Non-u.s. Gov't Research Support, N.i.h., Extramural Research Support, U.s. Gov't, Non-p.h.s. Journal Article Review

Available at Journal of biomechanics - from nih.gov

Abstract: Sickle cell anemia (SCA) is an inherited blood disorder that causes painful crises due to vaso-occlusion of small blood vessels. The primary cause of the clinical phenotype of SCA is the intracellular polymerization of sickle hemoglobin resulting in sickling of red blood cells (RBCs) in deoxygenated conditions. In this review, we discuss the biomechanical and biorheological characteristics of sickle RBCs and sickle blood as well as their implications toward a better understanding of the pathophysiology and pathogenesis of SCA. Additionally, we highlight the adhesive heterogeneity of RBCs in SCA and their specific contribution to vaso-occlusive crisis.

79. Pediatric sickle cell disease: past successes and future challenges.

Author(s): Meier, Emily Riehm; Rampersad, Angeli

Source: Pediatric research; Jan 2017; vol. 81 (no. 1-2); p. 249-258

Publication Type(s): Historical Article Journal Article Review

Abstract: Once a fatal disease of childhood, more than 95% of patients born today with sickle cell disease (SCD) in developed countries are expected to survive into adulthood, largely because of improvements in supportive and preventive care (newborn screening, penicillin prophylaxis, transcranial Doppler (TCD) screening). Hydroxyurea (HU) therapy, the only oral medication currently available to prevent SCD complications, has become more widespread over the past 20 y. The NHLBI recommends that HU be offered to all patients with HbSS beginning at 9 mo of age, and the recently published Abnormal TCD with Transfusions Changing to HU (TWiTCH) trial has shown HU as an acceptable alternative to transfusion therapy for patients at high risk of stroke. While hematopoietic stem cell transplant (HSCT) is a curative option for SCD, less than 25% of patients have a suitable donor. Alternative stem cell sources from unrelated donors and haplo-identical donors are currently under investigation as are gene therapy trials. This review will focus on early efforts to elucidate SCD pathophysiology as well as supportive and preventive care improvements. Findings from recent multi-center studies (Silent Infarct Transfusion (SIT) Trial and TWiTCH) will be summarized. Finally, HSCT trials and gene therapy will be reviewed.

Red Cell and Platelet Disorders

1. Efficacy and safety of thrombopoietin receptor agonists in children with chronic immune thrombocytopenia: A metaanalysis

Author(s): Guo J.-C.; Zheng Y.; Huang X.-H.; Zhong L.-P.; Zhou H.-B.; Xie D.-L.; Lou Y.-L.; Zhou H.; Chen H.-T.; Huang Y.

Source: Oncotarget; 2018; vol. 9 (no. 6); p. 7112-7125

Publication Type(s): Article

Available at Oncotarget - from Europe PubMed Central - Open Access

Abstract: Background and Aim: Thrombopoietin receptor agonists (TPO-RAs) have been shown to be safe and effective for adults with chronic immune thrombocytopenia (ITP). The aim of this meta-analysis is to assess the efficacy and safety of thrombopoietin receptor agonists for children with chronic ITP. Materials and Methods: Clinical randomized controlled trials (RCTs) evaluating the efficacy and safety of TPO-RAs in pediatric ITP patients published up to June 2017 were retrieved from PubMed, Cochrane Library, and Embase databases. Relevant data were extracted, and the Physiotherapy Evidence Database scale was used to assess the methodological quality. Stata/SE 12.0 was used to perform a meta-analysis. Results: Seven RCTs were included, with 238 patients and 107 patients in the TPORA group and the control group, respectively. Assessing efficacy, better results were found in the TPO-RA group for the rate of overall platelet response, durable response, and rescue medication needed. Furthermore, the TPO-RA group yielded superior results in the incidence of clinically significant bleeding events but had a comparable result in the incidence of any bleeding events and severe bleeding events. No significant difference was found between the two groups in health-related quality of life and parental burden. Assessing safety, no significant difference was found between the two groups in the incidence of any adverse events and severe adverse events. Conclusions: TPO-RAs are effective and safe agents for the treatment of chronic ITP in pediatric patients. Eltrombopag appears to be better than romiplostim in terms of the rate of rescue medication needed and clinically significant bleeding events.

2. Osmotic gradient ektacytometry: A valuable screening test for hereditary spherocytosis and other red blood cell membrane disorders.

Author(s): Llaudet-Planas, E; Vives-Corrons, J L; Rizzuto, V; Gómez-Ramírez, P; Sevilla Navarro, J; Coll Sibina, M T; García-Bernal, M; Ruiz Llobet, A; Badell, I; Velasco-Puyó, P; Dapena, J L; Mañú-Pereira, M M

Source: International journal of laboratory hematology; Feb 2018; vol. 40 (no. 1); p. 94-102

Publication Type(s): Journal Article

Abstract:INTRODUCTIONNew generation osmotic gradient ektacytometry has become a powerful procedure for measuring red blood cell deformability and therefore for the diagnosis of red blood cell membrane disorders. In this study, we aim to provide further support to the usefulness of osmotic gradient ektacytometry for the differential diagnosis of hereditary spherocytosis by measuring the optimal cutoff values of the parameters provided by this technique.METHODSA total of 65 cases of hereditary spherocytosis, 7 hereditary elliptocytosis, 3 hereditary xerocytosis, and 171 normal controls were analyzed with osmotic gradient ektacytometry in addition to the routine red blood cell laboratory techniques. The most robust osmoscan parameters for hereditary spherocytosis diagnosis were determined using receiver operating characteristic curve analysis.RESULTSThe best diagnostic criteria for hereditary spherocytosis were the combination of decreased minimal elongation index up to 3% and increased minimal osmolality point up to 5.2%

when compared to the mean of controls. Using this established criterion, osmotic gradient ektacytometry reported a sensitivity of 93.85% and a specificity of 98.38% for the diagnosis of hereditary spherocytosis.CONCLUSIONOsmotic gradient ektacytometry is an effective diagnostic test for hereditary spherocytosis and enables its differential diagnosis with other red blood cell membrane diseases based on specific pathology profiles.

3. Utility of the immature platelet fraction in pediatric immune thrombocytopenia: Differentiating from bone marrow failure and predicting bleeding risk.

Author(s): McDonnell, Alicia; Bride, Karen L; Lim, Derick; Paessler, Michele; Witmer, Char M; Lambert, Michele P

Source: Pediatric blood & cancer; Feb 2018; vol. 65 (no. 2)

Publication Type(s): Clinical Trial Journal Article

Abstract:BACKGROUNDDifferentiating childhood immune thrombocytopenia (ITP) from other cause of thrombocytopenia remains a diagnosis of exclusion. Additionally factors that predict bleeding risk for those patients with ITP are currently not well understood. Previous small studies have suggested that immature platelet fraction (IPF) may differentiate ITP from other causes of thrombocytopenia and in combination with other factors may predict bleeding risk.METHODSWe performed a retrospective chart review of thrombocytopenic patients with an IPF measured between November 1, 2013 and July 1, 2015. Patients were between 2 months and 21 years of age with a platelet count 5.2% differentiated ITP from BMF with 93% sensitivity and 91% specificity. Absolute immature platelet number (AIPN) was significantly lower in ITP patients with severe to life-threatening hemorrhage than those without, despite similar platelet counts. On multivariate analysis, an IPF < 10.4% was confirmed as an independent predictor of bleeding risk at platelet counts <10 × 109 /l in patients with ITP.CONCLUSIONSIPF measurement alone has utility in both the diagnosis of ITP and identifying patients at increased risk of hemorrhage. Further study is required to understand the pathophysiological differences of ITP patients with lower IPF/AIPN.

4. Benefits of Curcumin Supplementation on Antioxidant Status in beta-Thalassemia Major Patients: A Double-Blind Randomized Controlled Clinical Trial

Author(s): Nasseri E.; Mohammadi E.; Zand H.; Tamaddoni A.; Qujeq D.; Zayeri F.

Source: Annals of Nutrition and Metabolism; Jan 2018; vol. 71 (no. 3); p. 136-144

Publication Type(s): Article

Available at Annals of Nutrition and Metabolism - from EBSCO (MEDLINE Complete)

Abstract: Background: beta-Thalassemia major, the most common inherited anemia in the world, is associated with imbalance in the oxidant-antioxidant system. The objective of this study was to evaluate the efficacy of curcumin supplementation on markers of oxidative stress in patients with beta-Thalassemia. Methods: This double-blind randomized controlled clinical trial was performed on 61 beta-thalassemia major patients. Subjects in the curcumin group received two 500 mg curcumin capsules daily and patients in the placebo group took 2 placebo capsules daily for 12 weeks. Dietary intakes and biochemical parameters were assessed at the beginning and the end of intervention. Results: At the end of the study, serum malondialdehyde (MDA), total and direct bilirubin significantly decreased ($p = 0.002$, $p < 0.001$, and $p < 0.001$, respectively) and total antioxidant capacity significantly increased ($p = 0.005$) in the curcumin group. Based on the analysis of covariance, a significant reduction in MDA, total and direct bilirubin was also detected in the curcumin group when compared to the placebo group ($p = 0.001$, $p = 0.039$, and $p = 0.013$,

respectively). Changes in hemoglobin, serum iron, ferritin, catalase, and vitamin E were not significant in any of the 2 groups. Conclusions: Curcumin supplementation in combination with deferoxamin improved the antioxidant status in beta-thalassemia major patients. Curcumin may be useful for the relief of metabolic complications in these patients.

5. Hydroxyurea for lifelong transfusion-dependent β-thalassemia: A meta-analysis.

Author(s): Algiraigri, Ali H; Wright, Nicola A M; Paolucci, Elizabeth Oddone; Kassam, Aliya

Source: Pediatric hematology and oncology; Jan 2018 ; p. 1-14

Publication Type(s): Journal Article

Abstract:OBJECTIVEChronic blood transfusion remains the most feasible therapeutic option for lifelong transfusion-dependent β-thalassemia (lifelong TDβT). However, it is associated with serious risks and complications. Hydroxyurea (HU), an oral chemotherapeutic drug, is expected to increase hemoglobin levels, thereby minimizing the burden of blood transfusion and its complications. Growing literature over the last twenty years suggests promising results of the use HU in lifelong TDβT; however, its role and safety remain unanswered questions. The objective of this study was to evaluate the clinical efficacy and safety of HU in patients with lifelong TDβT.METHODSMEDLINE, EMBASE, Cochrane databases, and major preceding conferences for studies that assessed HU in lifelong TDβT patients were searched. The effect size was estimated as a proportion (responder/sample size).RESULTSEleven observational studies, collectively involving 859 patients, fulfilled eligibility criteria. HU was associated with a significant decrease in transfusion need with complete and overall (≥50%) response rates of 26% [95% confidence interval (CI), 13-41%] and 60% (95% CI, 41-78%), respectively. No serious adverse effects were reported. All of the studies had several limitations, such as lack of a comparison group.CONCLUSIONHU appears to be effective, well tolerated; however, large randomized clinical trials should be done to confirm such findings.

6. Thalassaemia.

Author(s): Taher, Ali T; Weatherall, David J; Cappellini, Maria Domenica

Source: Lancet (London, England); Jan 2018; vol. 391 (no. 10116); p. 155-167

Publication Type(s): Journal Article Review

Abstract: Inherited haemoglobin disorders, including thalassaemia and sickle-cell disease, are the most common monogenic diseases worldwide. Several clinical forms of α-thalassaemia and β-thalassaemia, including the co-inheritance of β-thalassaemia with haemoglobin E resulting in haemoglobin E/β-thalassaemia, have been described. The disease hallmarks include imbalance in the α/β-globin chain ratio, ineffective erythropoiesis, chronic haemolytic anaemia, compensatory haemopoietic expansion, hypercoagulability, and increased intestinal iron absorption. The complications of iron overload, arising from transfusions that represent the basis of disease management in most patients with severe thalassaemia, might further complicate the clinical phenotype. These pathophysiological mechanisms lead to an array of clinical manifestations involving numerous organ systems. Conventional management primarily relies on transfusion and iron-chelation therapy, as well as splenectomy in specific cases. An increased understanding of the molecular and pathogenic factors that govern the disease process have suggested routes for the development of new therapeutic approaches that address the underlying chain imbalance, ineffective erythropoiesis, and iron dysregulation, with several agents being evaluated in preclinical models and clinical trials.

7. Eltrombopag versus romiplostim in treatment of children with persistent or chronic immune thrombocytopenia: a systematic review incorporating an indirect-comparison meta-analysis.

Author(s): Zhang, Jiaxing; Liang, Yi; Ai, Yuan; Li, Xiaosi; Xie, Juan; Li, Youping; Zheng, Wenyi; He, Rui

Source: Scientific reports; Jan 2018; vol. 8 (no. 1); p. 576

Publication Type(s): Journal Article

Available at Scientific reports - from Nature Publishing Group - Open Access

Available at Scientific reports - from Europe PubMed Central - Open Access

Available at Scientific reports - from nih.gov

Abstract: In absence of direct comparison, we conducted an indirect-comparison meta-analysis to evaluate the efficacy and safety of thrombopoietin-receptor agonists(TPO-RAs) in treatment of pediatric persistent or chronic immune thrombocytopenia(ITP). PubMed, Embase, Cochrane Library, Clinical Trials.gov, China National Knowledge Infrastructure, and Chinese Biomedical Literature Database were searched from their earliest records to May 2017. Randomized controlled trials comparing the TPO-RAs with placebo in pediatric ITP were included. Outcomes included overall response rate(primary), durable response, overall or clinically significant bleeding, the proportion of patients receiving rescue medication, and safety. Five randomized placebo-controlled studies(N = 261) were analyzed. The overall response[Risk Ratio(RR) 0.57, 95% confidence interval(CI) 0.21-1.56], the incidence of adverse events (RR 0.96, 95%CI 0.66-1.39), durable response(RR 2.48, 95%CI 0.31-19.97), and the proportion of patients receiving rescue treatment(RR 0.73, 95%CI 0.20-2.73) were similar between eltrombopag and romiplostim group. Nevertheless, eltrombopag might have lower risk of overall bleeding(RR 0.43, 95%CI 0.23-0.80) and clinically significant bleeding(RR 0.33, 95%CI 0.12-0.89) than romiplostim. This meta-analysis suggests that eltrombopag might be similar to romiplostim in efficacy and safety, but seems to reduce the risk of bleeding compared to romiplostim. Furthermore, cost of the treatment, comorbidity of patients and drug compliance should also be considered in clinical decision making.

8. Sotatercept with long-term extension for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes: a phase 2, dose-ranging trial.

Author(s): Komrokji, Rami; Garcia-Manero, Guillermo; Ades, Lionel; Prebet, Thomas; Steensma, David P; Jurcic, Joseph G; Sekeres, Mikkael A; Berdeja, Jesus; Savona, Michael R; Beyne-Rauzy, Odile; Stamatoullas, Aspasia; DeZern, Amy E; Delaunay, Jacques; Borthakur, Gautam; Rifkin, Robert; Boyd, Thomas E; Laadem, Abderrhamane; Vo, Bond; Zhang, Jennie; Puccio-Pick, Marie; Attie, Kenneth M; Fenaux, Pierre; List, Alan F

Source: The Lancet. Haematology; Jan 2018

Publication Type(s): Journal Article

Abstract:BACKGROUNDMyelodysplastic syndromes are characterised by ineffective erythropoiesis leading to anaemia. Sotatercept (ACE-011) is a novel activin receptor type IIA fusion protein that acts as a ligand trap to neutralise negative regulators of late-stage erythropoiesis. The aim of the study was to establish a safe and effective dose of sotatercept for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes.METHODSThis open-label, multicentre, dose-ranging, phase 2 trial took place at 11 treatment centres in the USA and France. Eligible patients were aged 18 years or older, had International Prognostic Scoring System-defined low-risk or intermediate-1-risk myelodysplastic syndromes, had anaemia requiring red blood cell (RBC) transfusions, and were ineligible for, or refractory to, erythropoiesis-stimulating agents (ESAs). Patients were not eligible if they had chromosome 5q deletion myelodysplastic syndromes without documented failure of lenalidomide. Patients were randomly assigned to receive either 0·1 or 0·3 mg/kg sotatercept

subcutaneously, using a permuted-block method with stratification for serum erythropoietin concentration and transfusion burden. Patients were assigned to 0·5, 1·0, and 2·0 mg/kg groups in a non-randomised fashion. The primary efficacy endpoint was the proportion of patients who achieved haematological improvement-erythroid (HI-E), according to International Working Group 2006 criteria. Efficacy and safety analyses were done in the intention-to-treat population. This trial is registered at ClinicalTrials.gov, number NCT01736683 and at EU Clinical Trials Register, number 2012-002601-22, and is ongoing.FINDINGSBetween Dec 5, 2012, and July 22, 2015, 74 patients were enrolled into the study (seven to receive 0·1 mg/kg sotatercept, six to 0·3 mg/kg, 21 to 0·5 mg/kg, 35 to 1·0 mg/kg, and five to 2·0 mg/kg). 36 (49%; 95% CI 38-60) of 74 patients achieved HI-E; 29 (47%; 95% CI 35-59) of 62 patients with a high transfusion burden achieved HI-E (RBC-transfusion reduction from baseline of 4 or more units for at least 56 days), and seven (58%; 95% CI 32-81) of 12 patients with a low transfusion burden achieved HI-E (haemoglobin increase of 1·5 g/dL or more sustained for at least 56 days in the absence of transfusions). The most commonly reported adverse events were fatigue in 19 (26%) of 74 patients and peripheral oedema in 18 (24%) of 74 patients. Grade 3-4 treatment-emergent adverse events (TEAEs) were reported in 25 (34%) of 74 patients; four (5%) patients had grade 3-4 TEAEs that were considered to be treatment related. The most common grade 3-4 TEAEs were lipase increase and anaemia, which each occurred in three (4%) of 74 patients. 17 (23%) of 74 patients had at least one serious TEAE, and one patient died from a treatment-emergent subdural haematoma due to a fall.INTERPRETATIONSotatercept, a novel activin-receptor fusion protein, was well tolerated and effective for the treatment of anaemia in patients with lower-risk myelodysplastic syndromes in whom previous ESA treatment had failed. Treatment with sotatercept could be beneficial for these patients who have few available treatment options.FUNDINGCelgene Corporation.

9. Comparison of up-front treatments for newly diagnosed immune thrombocytopenia -a systematic review and network meta-analysis.

Author(s): Arai, Yasuyuki; Jo, Tomoyasu; Matsui, Hiroyuki; Kondo, Tadakazu; Takaori-Kondo, Akifumi

Source: Haematologica; Jan 2018; vol. 103 (no. 1); p. 163-171

Publication Type(s): Journal Article

Available at Haematologica - from HighWire - Free Full Text

Available at Haematologica - from Europe PubMed Central - Open Access

Available at Haematologica - from EBSCO (MEDLINE Complete)

Abstract: Corticosteroids such as prednisolone and dexamethasone have been established as up-front therapy for the treatment of newly diagnosed immune thrombocytopenia. Recent studies have indicated that other treatments such as rituximab or thrombopoietin receptor agonist can also be effective choices. We performed a systematic review and network meta-analysis to establish a clinically meaningful hierarchy of efficacy and safety of treatments for newly diagnosed primary immune thrombocytopenia in adults. Randomized controlled trials evaluating medical treatments for newly diagnosed immune thrombocytopenia were included. Reviewers independently extracted data and assessed the risk of bias. The main outcome was the sustained response (platelet count >30×109/L for 3-6 months after completion of treatments), while overall response (platelet count >30×109/L for 2-4 weeks after initiation of the up-front treatment) and therapy-related adverse events were the secondary endpoints. A total of 21 randomized controlled trials (1898 patients) were included in this study. Our main findings were a significantly better sustained response in the recombinant human thrombopoietin+dexamethasone and rituximab+dexamethasone arms compared to those of conventional therapies (prednisolone and dexamethasone monotherapy). Moreover, recombinant human thrombopoietin+dexamethasone and +prednisolone improved early

overall response compared to prednisolone, dexamethasone, and rituximab-containing regimens. Therapy-related adverse events showed similar profiles and were tolerable in all treatment arms. Regimens containing recombinant human thrombopoietin agonist may be beneficial up-front therapies in addition to the conventional corticosteroid monotherapies. Future head-to-head trials including these regimens and rituximab-containing treatments are necessary in order to overcome the limitations of the small number in our study and determine the most suitable initial therapies for newly diagnosed immune thrombocytopenia.

10. Chronic immune thrombocytopenia in children: New therapeutic options

Author(s): Rossi F.; Matarese S.M.R.; Corvino F.; Nobili B.

Source: Italian Journal of Pediatrics; 2017; vol. 43

Publication Type(s): Conference Abstract

Available at Italian Journal of Pediatrics - from BioMed Central

Available at Italian Journal of Pediatrics - from Europe PubMed Central - Open Access

Abstract: Immune thrombocytopenia (ITP) in children is defined as an autoimmune disorder characterized by isolated thrombocytopenia in the absence of other causes or disorders that are associated with thrombocytopenia. Newly diagnosed or "acute" ITP is defined as lasting <3 months, "persistent" lasting up to 12 months, and "chronic" lasting beyond 12 months in which a spontaneous remission is not achieved or in which patients do not achieve a response off therapy. Despite the vast majority of children with ITP will experience resolution, one-third of children will demonstrate thrombocytopenia at 12 months post-diagnosis consistent with chronic ITP [1-3]. Currently available therapeutic agents may provide a transient increase in platelet counts. This may be associated with diminished bleeding in some children. Other collateral benefits may be seen in some families such as less parental anxiety and greater support for children to participate in social activities [4]. Treatments for chronic ITP largely overlap with the therapeutic agents utilized for the treatment of acute ITP, including intravenous immunoglobulin, anti-D immunoglobulin, and corticosteroids [5,6]. The list of agents also includes a variety of agents such as vincristine, danazol, mycophenolate mofetil, and dapsone utilized as monotherapy or in various combinations [7, 8]. Rituximab and splenectomy remain as options.However, many of these treatments are not ideal in children with chronic ITP. Platelet response rates and durability of platelet responses with rituximab treatment are variable and the risk of mortality secondary to sepsis and thromboembolic events with splenectomy is low but real [9,10]. The thrombopoietin (TPO) is a lineage-specific cytokine that stimulates the production of megakaryocytes and platelets. Two TPO receptor agonists (TPO-RAs), romiplostim and eltrombopag, are currently Food and Drug Administration (FDA) approved for adults with chronic ITP. Eltrombopag is also approved for children >1 year. In a randomized phase I/II trial of pediatric patients with primary ITP for >6 months, 88% of patients receiving romiplostim maintained a platelet count >50 x 109/l for a median of 7 weeks compared to zero patients in the placebo group [5]. Results from eltrombopag randomized clinical trials showed that approximately 40% of patients were able to achieve a platelet count >50 x 109/l for the majority of study visits compared to 0-3% of patients in the placebo group [11-14]. Currently, TPO-RAs represent a new therapeutic option for children with chronic ITP. In the future, TPO-RAs may offer an important therapeutic option for other thrombocytopenias.

11. Stem cell transplantation for congenital dyserythropoietic anemia. a retrospective study on behalf of severe aplastic anemia working party of the European Blood and Marrow Transplantation Group (EBMT)

Author(s): Miano M.; Eikema D.-J.; Van 'T Veer P.J.; Aljurf M.; Maertens J.; Ozturk G.; De Heredia C.D.; Wolfl M.; Halkes C.J.M.; Schulz A.; Socie G.; Vettenranta K.; Skorobogatova E.; Zecca M.; Markiewicz M.; Rovira M.; Sierra J.; Cetinkaya D.; Antmen B.; Dalle J.-H.; Giardino S.; Al-Seraihy A.; Hamladji R.-M.; Kitra-Roussou V.; Nasa G.L.; Krivan G.; De Latour R.P.; Dufour C.

Source: Blood; Dec 2017; vol. 130

Publication Type(s): Conference Abstract

Abstract:INTRODUCTION Congenital Dyserythropoietic Anemias (CDA) are a group of heterogeneous bone marrow disorders characterized by anemia, ineffective erythropoiesis and specific cytomorphological features involving bone marrow late erythroblasts. Patients may also show some dysmorphisms involving fingers and nails. In the last few years genetic mutation explaining most cases of CDA have been identified. The management of the disease is generally limited to blood transfusion and iron chelation. Some report have shown the efficacy of stem cell transplantation (SCT) as the only curative option for this disease, however data from literature is scarce and limited to a very small number of cases In this retrospective study we describe the outcome of Stem Cell Transplantation in patients with CDA reported in the EBMT data base. PATIENTS AND METHODS The study was conducted on behalf of Severe Aplastic Anemia Working Party (SAAWP) of the EBMT and was based on data of patients affected with CDA who underwent SCT and registered in the EBMT Data Base. Clinical information of the disease and details on transplant procedures and followup were collected by a specific form distributed to Centres participating in the study. RESULTS Between 1996-2016, 39 patients (22 males-17 females) whose median age was 5.1 yo (range 0.9-38.2) underwent SCT from matched sibling donor (20, 51%), unrelated donor (17, 44%) or from other relatives (2, 5%) using bone marrow (30, 77%), peripheral blood (7, 18%) or cord blood (2, 5%) as cell source. All patients but one received a myeloblative regimen. Patients' characteristics and transplants outcome details are shown in Table 1. Median days to neutrophils and platelets engraftment were 21 and 34, respectively. Secondary graft failure occurred in 8 patients (20%). Median follow-up was 44 months (range 13-71). Overall survival at 36 months was 70%. Patients who were transplanted with iron overload and who were transplanted from unrelated donor had a significantly inferior outcome (36 month OS: 51% vs 92%, p =0.05 and 45% vs 90%, p 0.007, respectively). CONCLUSION To the best of our knowledge, this is the largest reported cohort of patients transplanted for CDA showing that family donor transplants have a better outcome and that iron overload negatively affects the procedure as reported in other red cell disorders.

12. Integration of a heparin-induced thrombocytopenia Order-Set (HITOS): A retrospective study

Author(s): Tsui E.; Jaresova A.; Berndsen J.; Dunbar N.M.; Ornstein D.L.; Drescher M.

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Abstract: Introduction: Heparin-induced thrombocytopenia (HIT) may occur after exposure to heparin containing products. When HIT is suspected, early recognition and diagnosis is crucial due to the risk for developing a life-threatening thrombotic event that can lead to substantial morbidity and even death.However, making the diagnosis of HIT is challenging due to a high false positive rate associated with most widely used screening tests for HIT. Therefore, clinical assessment of the likelihood of HIT is essential to help guide the decision to order a HIT laboratory test and to make changes in anticoagulation management. In 2014, we integrated a new custom HIT Order-Set (HITOS) with the EPIC electronic medical record (EMR) system. HITOS requires a clinician seeking to order a HIT laboratory test to input data to calculate a 4Ts pretest likelihood score for HIT. Recommendations are then automatically provided for proceeding or not with the HIT test and for anticoagulant management. Specifically, for patients with a low likelihood of HIT, HITOS

recommends continuing heparin without HIT testing. For patients with an intermediate or high likelihood, HITOS recommends discontinuing heparin in favor of an alternative anticoagulant and proceeding with HIT testing. Our study goals were to evaluate the effect of HITOS on patterns of HIT test ordering and on anticoagulation management in patients with suspected HIT. Methods: We performed a retrospective review of all inpatient charts in which an order for the laboratory test for HIT (heparin-PF4 antibody enzyme immunoassay) was recorded at Dartmouth Hitchcock Medical Center from December 2012 to December 2016. HITOS was launched in December 2014. Subjects were excluded from the study if their charts contained incomplete data, external laboratory results, previous documentation of a HIT diagnosis or duplicate testing . Data were extracted from the EMR for each study subject and included demographic information, clinical data, HIT test results and details of anticoagulation management before and after HIT laboratory testing. In the pre-HITOS group, the 4Ts score was applied retrospectively to assess the likelihood of HIT and was calculated independently by two study members. A score of <= 3 defined low likelihood for HIT; 4-5 points, intermediate; 6-8 points, high. The 4Ts score was obtained from the EMR in the post-HITOS group. Before and after HITOS comparisons were analyzed using the chi-square test for independence with a = 0.05. Results: A total of 465 EMR were reviewed; 401 subjects were included in the final analysis. The pre and post-HITOS groups included 213 and 189 subjects, respectively, with a similar median age (66 years, range 21 to 94 and 65 years, range 23 to 94). Pre-HITOS, a HIT test was ordered in 54% of low, 39% of intermediate and 7% of high likelihood cases. Post-HITOS, a HIT test was ordered in 30%, 57% and 14% of the respective cases (p <0.001 for each pre/post comparison). When there was at least an intermediate clinical likelihood for HIT, appropriate discontinuation of heparin at time of HIT testing occurred more frequently in the post-HITOS group (74% vs 66 %, respectively; p <0.001), and more patients in the post-HITOS group were accorded a clinical diagnosis of HIT than in the pre-HITOS group (11.1% vs 5.6%, respectively; p <0.05) group. Conclusions: Implementation of HITOS was associated with a decrease in HIT laboratory test ordering if the clinical likelihood for HIT was low and was associated with a higher rate of appropriate heparin discontinuation when the clinical likelihood of HIT was intermediate or high. Our results suggest that integration of HITOS may help refine the diagnostic process in patients with suspected HIT, though additional study will be required to evaluate the cost-effectiveness and effects on morbidity and mortality of this approach.

13. Diagnosis and management of heparin induced thrombocytopenia - Are we choosing wisely?

Author(s): Kopparthy P.; Basnet A.; Graziano S.; Roe C.A.

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Publication Type(s): Conference Abstract

Abstract: Introduction : Thrombocytopenia is a common problem in hospitalized patients. One of the rare but fatal causes of thrombocytopenia is Heparin Induced Thrombocytopenia (HIT), a complex immune disorder in which heparin leads to the production of IgG antibodies, targeting platelet factor 4 (PF4). Not diagnosing HIT when it is present or mistakenly diagnosing HIT when it is absent, both carry significant risks (eg, life-threatening thrombosis or life-threatening bleeding, respectively). Various institutional reviews have reported that clinicians tend to have a high suspicion and low threshold to order laboratory workup for HIT though the incidence of HIT is noted to be only 5%. The American Society of Hematology Choosing Wisely Guidelines 2014 recommend against testing for HIT in individuals at low risk, defined by a 4T score <= 3. The primary objective of our study was to examine compliance with guidelines at our institution. Secondary objectives were to assess correlation between 4T's score, HIT antibody and Serotonin Release Assay (SRA) in diagnosis of HIT, impact of Hematology consult on following appropriate guidelines. Methods: Patients with requests for HIT antibody testing between 1/1/2015 - 12/31/2016 were identified from laboratory records. A retrospective chart review was conducted on 92 patients who met criteria. Data collected included

admitting department, clinical probability based on 4T's score, result of HIT antibody including optical density (OD), result of SRA, placement of Hematology consult, initiation of novel anticoagulant (NOAC). Using the algorithm below (Fig 1) , compliance with guidelines was analyzed. Data were tabulated by means of simple frequencies for single items, or in 2- or 3-way combinations. Results: Of the 92 charts reviewed, 38 (41.3%) patients had a low clinical probability based on 4T's score and yet had HIT antibody test ordered (table 1). Of these, heparin was stopped in 21 (55.3%) patients and NOAC was initiated in 10 (26.3%) patients (table 2) which is not recommended as per existing guidelines. Interestingly, of the 38 patients with low probability, 19 (50.0%) had OD between 0.4 - 1.99 with 1 positive SRA. Among 43 (46.7%) patients with intermediate clinical probability, 29 (47.5%) patients were HIT positive. Of these, 18 patients with OD < 2 and 21 patients with OD between 0.4 - 1.99 had SRA ordered which is not in compliance with guidelines, however 6 of these patients had positive SRA. 11 (12%) of the 92 patients had high clinical probability, and of these, in patients with OD> 2, SRA was positive 100% of the times; where as in patients with OD between 0.4 - 1.99 SRA was positive only in 45.5% patients. Hematology oncology service was consulted for 44 (47.8%) patients with positive HIT of which 7 had high probability, 22 had intermediate probability and 15 had low clinical probability; heparin was stopped and NOAC was initiated in 5(71%), 12 (54%), and 8 (53%) patients in each of these groups respectively which once again is not in compliance with existing guidelines. Majority of patients were admitted to ICU, however only 3.8% of ICU patients who had HIT antibody ordered had confirmed diagnosis of HIT. Conclusion: Compliance with Choosing Wisely Guidelines and recommended diagnostic algorithm for HIT at our institution is low, and potentially associated with significant harm to the patient due to overtesting and overtreatment. Hematology Oncology consult did not necessarily improve compliance with guidelines, although decision about NOAC were made prior to consult in most cases. However, while there was concern for overdiagnosis and wasteful resources, our study also noted that there were few patients with low clinical probability and intermediate clinical probability with OD between 0.4-1.99 with positive SRA. Limitations of our study is the small sample size and single institution based data. (Table Presented).

14. Re-presentation to medical care due to adverse effects of intravenous immunoglobulin therapy in pediatric immune thrombocytopenia patients

Author(s): Grimes A.; Kirk S.E.; Olmsted T.; Lambert M.P.; Despotovic J.M.

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Abstract: Background : Immune Thrombocytopenia (ITP) is one of the most common acquired bleeding disorders affecting children, with an incidence rate of approximately 5-10 per 100,000 children per year. Intravenous immunoglobulin (IVIG) is an effective and widely employed frontline therapy for ITP; but is associated with substantial adverse effects, most commonly including headaches (~40%) and nausea/vomiting (5-26%). These may occur immediately following infusion or up to 72 hours later, often resulting in re-presentation to medical care. Additional diagnostic testing is often performed, including computed tomography (CT) imaging of the head, given concern for intracranial hemorrhage in these severely thrombocytopenic patients who have not yet responded to IVIG. Objective : To identify rates of re-presentation to medical care due to IVIG-associated adverse effects within a cohort of treated pediatric ITP patients, and to identify the impact of this re-presentation to care on patient safety, health-related quality of life (HRQoL), and healthcare-related costs. Methods : We completed a retrospective chart review, inclusive of all pediatric ITP patients receiving IVIG therapy at a large pediatric referral center within a 6-year timeframe from 2010 - 2016. Included patients were between the ages of 0 and 18 years, receiving IVIG for the primary indication of ITP at a dose of 1 g/kg/dose, and receiving the commercial IVIG product Gamunex-C

10% (Grifols). All patients not meeting these criteria were excluded in order to maximize homogeneity of evaluated patients. Pre-medication with acetaminophen and diphenhydramine is the standard of practice for IVIG administration within the institution. Results : Among the 473 ITP patients who received Gamunex-C at Texas Children's Hospital from 2010 - 2016, 133 (28%) experienced documented headache, nausea/vomiting, or both following IVIG infusion, consistent with published incidences. Among these patients, 101 (76%) sought medical care due to these symptoms. Of the 81 patients who had already been discharged, 54 (67%) re-presented for Urgent or Emergency Care services; while 27 (33%) called for medical advice or to obtain supportive prescriptions. Of the 20 patients remaining hospitalized, 100% presented as calls to the on-call physician, resulting in additional medical evaluation, often including laboratory or imaging evaluation. Among all patients re-presenting to medical care, 60 (59%) underwent additional laboratory testing, and 36 (36%) underwent CT imaging to evaluate for life-threatening intracranial bleeding. No CT evaluations revealed evidence of intracranial bleeding, and for all 101 patients re-presenting to medical care, symptoms fully resolved with supportive management. Conclusions : Nearly 1/3 of treated patients in our cohort experienced headache and/or nausea/vomiting, consistent with published incidences for Gamunex-C . Of these, 76% sought further medical care. Subsequent medical management ranged from supportive care only (41%) to full evaluation with repeat laboratory studies (59%) + CT imaging in many cases (36%). These findings implicate substantially increased healthcare-related costs in the form of laboratory, CT imaging, and emergency service expenses; as well as increased risk to these patients' health and safety, in the form of additional radiation exposure, infection risk, and potential exposure to unnecessary therapies. Formal evaluation of downstream HRQoL and costs is ongoing. Additionally, we believe that a standardized prophylactic post-medication strategy could prevent or significantly reduce re-presentation to medical care due to IVIG-associated headache and/or nausea/vomiting, thereby improving HRQoL and cost impact in this patient population; and a formal prospective trial of this strategy is planned. (Figure Presented).

15. A Canadian cost-effectiveness analysis for the treatment of immune thrombocytopenia: Assessing the relative value of with eltrombopag versus romiplostim

Author(s): Tremblay G.; Dolph M.; Forsythe A.; Roy A.; Neyra J.; El Ouagari K.

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Abstract: Background: Eltrombopag (EPAG) was evaluated as a second line treatment for adult chronic immune thrombocytopenia (ITP) in the 2005 Phase III RAISE randomized, placebo-controlled trial. More than 80% of patients reached satisfactory platelet counts within two weeks. However, the relative value of EPAG as a second line treatment for ITP remains to be formally assessed. Objective: This study aimed to estimate the cost-effectiveness of treating ITP with comparable thrombopoietin receptor agonists: EPAG versus Romiplostim (ROMI). Methods: A cost-effectiveness model was developed from a Canadian payer perspective. In the base case, Markov model was implemented to estimate the benefits and costs expected with each treatment over a lifetime time horizon. Three health states based on the clinical pathway and current guidelines for the treatment of ITP were included in the model: (1) on treatment, (2) treatment failure/discontinuation, and (3) mortality. As reducing bleeding is the therapeutic goal in ITP, bleeding rates were incorporated into the model. Pre-mortality, patients could experience three events: no bleeding, mild/moderate bleeding, or severe bleeding. Data on EPAG use were obtained from the EXTEND study, an open-label extension of four trials including RAISE. For ROMI, data were obtained from Phase III trials and a subsequent extension study. Lifetime overall survival was extrapolated by applying constant treatment-specific mortality rates derived from severe bleeding events and natural mortality rates.

As no health-related quality of life data were collected during the RAISE clinical trial, EPAG health state utilities were obtained from other relevant studies (Szende, 2010; Leontiadis, 2010; ROM NICE submission TA221). The costs of drugs (primary and secondary therapy), rescue medications, routine care, bleeding episodes, adverse events, and mortality were incorporated into the model. Costs, in Canadian dollars, were derived from the relevant pricing databases. Costs and benefits were discounted at 1.5% per year according to CADTH guidelines. Results: EPAG-treated patients gained 22.53 life years (LY) and 18.81 quality-adjusted life years (QALY) while those treated with ROMI gained 22.45 LYs and 18.80 QALYs. The total cost for EPAG treatment was estimated at $513,301 versus $805,025 for ROMI treatment. EPAG was dominant (lower cost, greater benefit) in terms of both costs per LY and costs per QALY. Sensitivity analyses supported base case findings. Deterministic sensitivity analysis predicted the greatest sensitivity to variations in the rates of severe bleeding, discontinuation, and natural mortality. The probabilistic sensitivity analysis demonstrated the probability of cost-effectiveness was 55.7% at both $25,000 and $50,000 thresholds and EPAG was therefore a reasonably efficient use of resources. In a subsequent cost-consequence analysis, EPAG patients experienced fewer severe bleeding events (0.05 versus 0.08 for ROMI) and, overall, their annual costs were lower ($65,514 versus $96,914 for ROMI). Conclusion: Both EPAG and ROMI has demonstrated significant improved in bleeding versus the standard of care in the phase 3 clinical trial.s These results were applied in the economic analysis and EPAG proved to be more cost-effective as compared to ROMI.

16. High incidence of true heparin-induced thrombocytopenia and heparin-induced thrombocytopenia antibody development in critically ill medical patients

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Publication Type(s): Conference Abstract

Abstract: Background: Thrombocytopenia is very prevalent in critically ill medical patients. Heparin-induced thrombocytopenia (HIT), which is a serious immunologic complication of heparin administration, is one of the major concerns. Diagnosis of HIT in critically ill patients is challenging due to concomitant illnesses. We previously reported the HIT cohort with the high proportion of critically ill medical patients (61.7%) in Thailand (Uaprasert N, etal. Blood Coagul Fibrinolysis 2013;24:261-8). However, data of the true incidence and risk factors for HIT in this particular population in Thailand are still lacking. In addition, the confirmatory assay is not readily available and unlikely to be useful for timely clinical management. Therefore, clinical predictors and screening assays are important for immediate clinical judgment. This study aimed to determine the incidence and define risk factors for HIT and HIT antibody (HIT-Ab) development as well as an appropriate clinical predicting model for HIT in critically ill medical patients. Methods: Consecutive critically ill medical patients who received heparins and were admitted in the intensive care unit (ICU), coronary care unit (CCU) and intensive coronary care unit (ICCU) at King Chulalongkorn Memorial Hospital between October 2013 and May 2017 were included in this study. Patients admitted in general wards who met one of the following criteria: 1) on mechanical ventilator 2) receiving inotropic agents 3) recent undergoing renal replacement therapy due to acute kidney injury and/or 4) APACHE II score > 25, were also included for analysis. Blood samples were collected between 6 and 8 days after heparin exposure. Patients died or discharged before day 6 after heparin exposure were excluded from the study. The rapid particle gel immunoassay (PaGIA) was used as the screening test for detecting antibodies against the heparin/platelet factor 4 complex. Subjects yielding positive PaGIA were sent for the confirmatory test using the in-house platelet aggregometry measuring heparin-induced platelet aggregation (HPA). Details of the medical history and hospital course of

individual patient were reviewed to obtain risk factors for HIT as well as to compute two well-defined clinical probability scores (4Ts and HIT expert probability, HEP). Results: There were 217 patients included for analysis. The average age was 64.9 +/- 18.7 (mean +/- standard deviation) years. The baseline platelet counts were 217 +/- 116 x 10 /L. A platelet fall >= 50% from baseline was found in 135 (62.2%) patients. The most common type of heparin administered was unfractionated heparin (165; 76%). HIT-Ab using PaGIA was detected in 52 (24%) patients, while true HIT was confirmed using HPA in 3 patients (1.38%). Most common underlying illnesses found in patients developing HIT-Ab were hypertension, coronary arterial disease and active infection. Acute stroke, a platelet fall >= 50% from baseline, 4Ts score of > 3 and HEP score of >= 2 were significantly associated with development of HIT-Ab in univariate analysis, while heparin types and hemodialysis were not statistically associated with HIT-Ab development. Notably, only acute stroke was significantly associated with HIT-Ab development in multivariate analysis (Odds ratio 6.56; 95% confidence interval 1.42-30.31, p=0.016). Conclusion: The incidence of HIT-Ab detected in critically ill medical patients in our cohort was comparable to most studies, while the incidence of true HIT in this cohort was apparently higher than previous reports, which their incidences were <= 0.5%. The reasons underlying the high incidence of true HIT in critically ill medical patients in Thailand remains elusive. Acute stroke is a significant risk for HIT-Ab development in critically ill medical patients receiving heparin. (Figure Presented).

17. Rates of severe bleeding are low in patients with MDS and severe thrombocytopenia and may be mitigated by tranexamic acid

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Abstract: Introduction: While thrombocytopenia is common and affects 29% of patients (pts) with MDS, severe thrombocytopenia (platelets (plt) <20x109 /L) affects approximately 10% of pts and is associated with bleeding and higher risk IPSS-R scores. Prophylactic and therapeutic plt transfusions are commonly administered to prevent bleeding in pts with MDS and severe thrombocytopenia but are inconvenient and associated with risks. Since the inception of the MDS registry in 2006 at our centre, we commonly administer tranexamic acid (TXA, 1-1.5 grams PO BID-TID) to thrombocytopenic pts with MDS to decrease minor mucosal bleeding and the use of plt transfusions for non-severe bleeds. The administration of prophylactic and/or therapeutic plt transfusions is at the discretion of the treating haematologist. Objective: To retrospectively audit the bleeding rates and transfusion requirements of pts with MDS and durable severe thrombocytopenia as related to TXA use, plt transfusions, and disease characteristics. Methods: All pts with MDS with durable severe thrombocytopenia (plt count <20x109 /L in >=50% of days over an 8-week period) treated at Sunnybrook Health Sciences Centre and registered in the prospective MDS registry were eligible. Bleeding events, rated with the World Health Organization bleeding scale were captured by registry and chart review. The highest grade bleed experienced by the patient was assigned once for each clinic visit documenting a bleeding event. Platelet transfusion frequency and quantity during the period of severe thrombocytopenia were obtained. Platelet transfusions were considered prophylactic (PROPH) if they occurred at a recurring time interval of <=2 weeks, and were considered therapeutic otherwise. Descriptive statistics are reported, and ANOVA or correlation coefficients were calculated where relevant. Results: Of 200 pts with severe thrombocytopenia at any time, 99 had durable severe thrombocytopenia and were included. Demographics are presented in Table 1. The pts were classified as receiving TXA alone (n=28), TXA + PROPH, (n=39), PROPH plts alone (n=19) and untreated (n=13). Median time from diagnosis to start of durable severe

thrombocytopenia was 0.9 years (IQR 0.2-2.2), duration was 27 weeks (IQR 16-49), and median plt count was 12x109 /L (IQR 9-16). Pts receiving TXA +/- PROPH plts had significantly higher rates of concurrent red blood cell transfusion dependence. With a median follow-up of 0.8 years (95% CI 0.6-1.2), actuarial survival was 0.9 years (95% CI 0.7-1.2). 9 9 9 68% of pts were prescribed TXA at any point with a median time from onset of severe thrombocytopenia of 5 weeks (IQR 0-13) and a median duration of 23 weeks (IQR 12-41). Only 32% and 23% of TXA alone and untreated pts respectively required therapeutic plt transfusions at any point with a median time between transfusions of 2.8 and 4.0 weeks respectively. The median number of plt transfusion events per 4-week period was 0 for TXA alone and untreated pts compared with 2.2 and 3.1 events for TXA + PROPH or PROPH alone (p<0.0001) (Table 2). During the period of severe thrombocytopenia, 82% (81/99) of pts had at least one bleeding event, and 5% (5/99) had a grade 4 bleeding event. There was a significant difference in grade 1 and 2 bleeding rates between groups, with the highest rates in pts on TXA +/- PROPH plts (Table 2). There was no significant difference in grade 3 or 4 bleeding rates between groups. Conclusions: Patients with MDS and durable severe thrombocytopenia at a Canadian tertiary care centre had low rates of major bleeding (5%) compared to what has been previously reported in the literature, but poor overall survival. Seventy-one percent of severely thrombocytopenic pts on TXA or no therapy required no therapeutic platelet transfusions for the duration of study follow-up. The benefit of TXA and/or prophylactic platelet transfusions for the prevention of bleeding would be best evaluated in the context of a randomized controlled trial. (Figure Presented).

18. Utility and patterns of vitamin b12 and folate testing in patients with isolated thrombocytopenia

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Abstract: Background:Deficiencies of vitamin B12 and folate are commonly considered in the differential diagnoses of thrombocytopenia. However, the utility of measuring vitamin B12 and folate levels during the evaluation of isolated thrombocytopenia is unclear. Methods:In this retrospective review, we studied the frequency of ordering vitamin B12 and folate levels among patients with isolated thrombocytopenia (platelet count < 150 x 10 /L without anemia or neutropenia) evaluated at our institution from 2015-2016. We also collected information on the specialty of the ordering clinician. Results:During the study period, 129 patients with isolated thrombocytopenia were evaluated by hematology (67.4%), inpatient medicine (inpatient internal medicine and emergency department physicians) (16.3%), outpatient internal medicine (9.3%), and other departments (7.0%). Vitamin B12 levels were tested in 57 (44.2%) patients, and of these a methylmalonic acid (MMA) was ordered for 13 (22.8%), all of which were normal. Three patients (5.3%) had low vitamin B12 levels (179, 148, 143 ng/L; normal 180-914 ng/L), but only one had an MMA performed, which was normal, indicating no vitamin B12 deficiency. The remaining two were ultimately diagnosed with idiopathic thrombocytopenic purpura and hypersplenism, respectively. Mean corpuscular volume (MCV) was tested in 128 of the patients, and of those 24 (18.8%) had macrocytosis. Of those with macrocytosis, 14 (58.3%) had vitamin B12 levels tested, compared with 41.3% of patients with normal MCV, though this was not statistically significant (P= 0.131). Folate levels were tested in 37 (28.7%) patients, and none were low. Of patients with macrocytosis, 37.5% had folate levels tested compared with 26.9% of those with normal MCV (P= 0.303). The ultimate causes of the patients' thrombocytopenia were determined to be: idiopathic thrombocytopenic purpura (37.2%), hypersplenism (14.7%), liver disease (7.0%), medication-induced (5.4%), other

causes (18.6%), and unknown (17.1%). In the unknown group, all patients had platelet counts > 100 x 10 /L and therefore did not meet diagnostic criteria for idiopathic thrombocytopenic purpura based on the practice guidelines of the American Society of Hematology. Vitamin B12 testing was most frequently ordered by clinicians from internal medicine (75.0%), followed by inpatient medicine (42.9%) and hematology (41.4%). Folate testing was most frequently ordered by clinicians from inpatient medicine (33.3%), hematology (29.9%), and internal medicine (8.3%). Conclusion:At our institution, testing for vitamin B12 and folate levels is a common practice in the evaluation of isolated thrombocytopenia. However, no patient was diagnosed to have thrombocytopenia associated with vitamin B12 or folate deficiency during the time period examined. Though these tests are neither expensive nor invasive, when repeated needlessly over time additive costs and extraneous data can cause confusion and misdirection in patient care. Therefore, given the extremely low likelihood of vitamin B12 deficiency causing isolated thrombocytopenia, it would seem best to consider testing only if there are other findings suggestive of vitamin B12 or folate deficiency. Though this advice is most relevant to hematology, it is also important for other specialties, particularly general internal medicine, to consider.

19. Exploring the clinical utility of renal safety biomarkers during iron chelation therapy in patients with beta-thalassemia and other anemias

Author(s): Cappellini M.D.; Quebe-Fehling E.; Pallaud C.; Dieterle F.; Porter J.B.

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Abstract: Background: Close monitoring of renal function is recommended before and during treatment with the iron chelators deferasirox and deferoxamine (DFO), by assessment of serum creatinine (SCr) and estimated creatinine clearance. To identify patients at increased risk for acute kidney injury while on therapy, efforts are focused on protein biomarkers to predict changes in renal function before SCr increases and to understand the pathophysiology involved. Alpha-1 microglobulin (alpha1M), beta-2 microglobulin (beta2M), retinol-binding protein (RBP), and (urinary) cystatin C increases may reflect proximal tubular dysfunction. Changes in kidney injury molecule-1 (KIM-1), lipocalin-2 (also called NGAL), N-acetyl-betaglucosaminidase (NAG), clusterin, osteopontin, and tissue inhibitor of metalloproteinase-1 (TIMP-1) may reflect localized pathological processes in the renal nephron. KIM-1 is upregulated dramatically upon epithelial injury and is specific for the proximal tubule. Urinary total protein, microalbumin, and immunoglobulin G (IgG) may reflect either glomerular or tubular injury. The current exploratory analysis assessed 19 renal protein biomarkers as early indicators for an increased risk of acute renal dysfunction in chelated, transfusion-dependent patients with beta-thal or other anemias. Objectives were to explore: 1) changes in biomarker profiles over time; 2) correlations between baseline biomarker levels and changes in SCr during treatment; 3) the correlation of changes in biomarker levels with changes in SCr during treatment; 4) correlations between early biomarker changes during treatment with subsequent changes in serum creatinine. Methods: Archived urine samples collected at baseline and every 3-6 months during two deferasirox clinical trials (comparative 1-year 107 study of beta-thal patients randomized to deferasirox or DFO; non-comparative 2-year 108 study including beta-thal or other anemia [MDS, DBA, rare anemias] patients, excluding SCD) were used. All patients enrolled were aged >=2 years, received at least 8 blood transfusions/year, and had LIC >=2 mg Fe/g dw. No patient had baseline SCr >upper limit normal. Patients at risk of acute renal dysfunction were defined as having SCr increased >33% from baseline on >=2 consecutive visits during the trials. ROC curves were generated by treatment and by underlying disease to determine whether urinary renal markers at baseline (pre-treatment) or change from baseline could predict an increased risk of acute renal dysfunction. Results: 586 beta-thal patient samples were assessed from the comparative trial (n=296

deferasirox, n=290 DFO) and 184 from the non-comparative trial (n=85 beta-thal; n=99 other non-beta-thal anemias [MDS, n=47; DBA, n=30; other rare anemias, n=22]). No significant progressive changes in any renal biomarkers were observed; including acute renal injury (KIM-1, NGAL) and inflammatory (clusterin, osteopontin) biomarkers. Biomarker levels at baseline showed little/no correlation with changes in SCr. Area under the ROC curve (AUC) values were 0.45-0.60, suggesting limited predictive value for urinary renal biomarkers at baseline (pre-treatment) to predict an increased risk of acute renal dysfunction (1.0 = a perfect test, 0.5 = no better than a random test). Weak, though consistent positive correlations were identified between logged fold-change from baseline for biomarkers of renal protein reabsorption and glomerular filtration (alpha1M, beta2M, RBP, microalbumin, total protein, IgG) versus relative change in SCr from baseline over time (r=0.1-0.3) across patient groups. Better associations were identified in non-beta-thal patients. Confirmed increase in SCr had the most association with RBP (Fig 1A) and beta2M (Fig 1B) in deferasirox-and DFO-treated patients, respectively. In the non-comparative trial, AUC values were 0.4-0.6 for beta-thal patients; most association with NGAL (Fig 1C). In patients with other anemias, nine renal biomarkers had AUCs >0.6; most association with alpha1M (Fig 1D). Conclusions: Without definitive associations with SCr, findings do not support the clinical utility of any of the 19 renal protein biomarkers assessed for monitoring kidney function. The absence of progressive renal biomarker changes at the population level indicates that chelation therapy with deferasirox or DFO did not lead to acute/chronic or progressive renal dysfunction in these studies.

20. Emergency management of patients with immune thrombocytopenia and severe bleeding

Author(s): Mithoowani S.; Shah N.; Ejaz R.; Barty R.; Li N.; Nazy I.; Kelton J.G.; Arnold D.M.

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Abstract: Background Severe bleeding is a rare but potentially life-threatening complication of immune thrombocytopenia (ITP). In this study, we describe the management and clinical outcomes of patients with ITP presenting to the emergency room (ER) with thrombocytopenia and severe bleeding over a 9-year period from 3 Canadian tertiary care centers. Methods Patients with ITP who had severe thrombocytopenia (platelets <20 x10 /L) and severe bleeding, and who presented to any of 3 hospital emergency rooms (ER) affiliated with McMaster University in Hamilton, Canada between 2008 and 2016 were included in this retrospective study. We reviewed ER and hospital records and extracted demographic data, platelet counts, and all treatments received until discharge or day 10 of hospital admission. We described all bleeding and thrombotic events. Bleeding was graded from 0 (none) to 2 (severe) at one or more anatomical sites using the ITP Bleeding Score (Page et al, Br J Haematol 2007). Patients with skin or oral mucous membrane bleeding only were excluded. Data from a sample of 41 charts were extracted in duplicate (by SM and NS) to ensure consistency; discrepancies were resolved by the principal investigator (D.M.A.). Data were summarized descriptively as frequencies (percentage), means (standard deviation [SD]), or medians (interquartile range [IQR]). Ethics approval was obtained from the Hamilton Integrated Research Ethics Board. Funding for this study was provided by a grant from the Platelet Disorder Support Association. Results Thirty-one patients had platelets <20 x10 /L with grade 2 bleeding. Mean (SD) age was 56 years (+/-24) and 16 patients (52%) were female. Twentythree patients (74%) had primary ITP; others had secondary ITP due to medications (n=2), systemic lupus erythematosus (n=2), malignancy (n=2), hepatitis (n=1), or other infection (n=1). Sixteen patients (52%) had newly-diagnosed ITP; 15 (48%) had known ITP and had previously received a median (IQR) of 3 (3-4) ITP therapies including splenectomy (n=7). Median (IQR) platelet count at presentation to the ER was 4 x10 /L (2-8 x10 /L). There were 37 ER visits among 31 patients. Sites of grade 2 bleeding at presentation to the ER were: GI (18/37 visits, 49%), epistaxis (10/37 visits, 27%), urinary (6/37 visits, 16%), gynecological (4/37 visits, 11%) and intracranial (4/37 visits, 11%). Patients were given a

median (range) of 2 (0-7) treatment modalities in hospital including corticosteroids (30/37 visits, 81%), intravenous immune globulin (25/37 visits, 68%) and platelet transfusions (17/37 visits, 46%). Other treatments were romiplostim (3/37 visits), tranexamic acid (3/37 visits); and emergency splenectomy, recombinant factor VIIa, Rh immune globulin, danazol, azathioprine and mycophenolate (1/37 visits each). Four patients experienced new or recurrent grade 2 bleeding in-hospital, including two deaths: a 76 year-old female with a platelet count of 11 x10 /L on warfarin who developed ICH (received 4 treatment modalities); and a 20-year-old male with a platelet count of 8 x10 /L and ICH (received 7 treatment modalities). Median (IQR) length of hospital admission was 4 (3-9) days for 29 admissions. Conclusions Severe bleeding in patients with ITP is a high risk situation that requires prompt intervention. Treatments and outcomes were variable. A standardized approach to the treatment of bleeding emergencies in ITP is needed.

21. Gene therapy for beta thalassemia: Preliminary results from the PHASE I/II tiget-bthal trial of autologous hematopoietic stem cells genetically modified with GLOBE lentiviral vector

Author(s): Marktel S.; Giglio F.; Ciceri F.; Cicalese M.P.; Calbi V.; Casiraghi M.; Ciotti F.; Aiuti A.; Scaramuzza S.; Lidonnici M.R.; Rossi C.; Mandelli G.; Calabria A.; Montini E.; Ferrari G.; Masera N.; D'Angelo E.; Mirra N.; Origa R.; Tartaglione I.; Milani R.; Gattillo S.; Coppola M.; Santoleri L.; Viarengo G.; Perrotta S.; Graziadei G.; Cappellini M.D.; Naldini L.

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Publication Type(s): Conference Abstract

Abstract: Gene therapy for transfusion dependent beta-thalassemia is based on the autologous transplantation of hematopoietic stem cells (HSCs) engineered by lentiviral vectors expressing a transcriptionally regulated human beta-globin gene.Gene therapy (GT) could represent an alternative to HSCT with the following potential advantages: use of autologous stem cells, tailored conditioning with no need for immune suppression post GT, no risk of GVHD or rejection.Our contribution to this field was devoted to the clinical development of a gene therapy protocol based on the high-titer vector GLOBE, a 3 generation self-inactivating lentiviral vector encoding for the human beta globin gene. Transfusion dependent beta thalassemia patients (any genotype) undergo peripheral blood stem cell harvest following mobilization with the lenograstim and plerixafor. After transduction of immuneselected autologous CD34+ cells and successful release of the frozen drug substance, patient undergo a conditioning regimen based on myeloablative treosulfan and thiotepa favoring efficient engraftment of corrected cells with reduced extra-medullary toxicity (TIGET-BTHAL; EudraCT number 2014-004860-39). The route of administration of gene modified HSCs is intraosseous in the posterior-superior iliac crests with the aim of enhancing engraftment and minimizing first-pass intravenous filter. Three days after gene therapy, previously collected unstimulated autologous peripheral blood leucocytes (1-10 x107 CD3+/kg) are reinfused intravenously to favor immune-reconstitution. After 2 years follow-up, patients will be followed up for a further six years in a long-term follow-up study. On the basis of extensive efficacy and safety preclinical studies the clinical trial TIGET-BTHAL was approved and started in 2015 at Scientific Institute San Raffaele, Milan, Italy. The clinical study foresees treatment of 10 patients: 3 adults (group 1) followed by 3 patients aged 8-17 years (group 2) and 4 patients aged 3-7 years (group 3), with a staggered enrolment strategy based on evaluation of safety and preliminary efficacy in adult patients by an independent data safety monitoring board (DSMB) before inclusion of pediatric subjects. In March 2016 the DSMB approved enrolment of group 2 patients and, in September 2016, of group 3 patients. As of August 2017, seven patients (3 adults aged 31-35 years and 4 pediatric patients aged 6-13 years) with different genotypes (beta0/beta0, beta+/beta+ and beta0/beta+) have been treated with GLOBE-transduced CD34+ cells at a dose of 16x106-19.5x106 cells/kg and a vector copy number (VCN)/cell ranging from 0.7 to 1.5. Median follow-up is 13 months (range 8-22).

The procedure was well tolerated by all patients, with no product-related adverse events, no evidence of replication competent lentivirus nor of abnormal clonal proliferation on regular peripheral blood and bone marrow analyses. Grade 3-4 adverse events or serious adverse events were principally of infectious origin as expected after a myeloablative autograft. Median time to neutrophil engraftment was 19 days (range 17-25) and to platelet engraftment 15 days (range 10-21). Multilineage engraftment of gene-marked cells was observed in peripheral blood and bone marrow, with a median of 0.58 (range 0.37-1.55) vector copy number/cell in GlyA+ bone marrow erythroid cells at 6 months post GT.Polyclonal vector integrations profiles have been detected in the first 3 patients tested. The three adult patients had a reduction of transfusion requirement but are still transfusion dependent at the last follow-up (22, 18 and 16 months respectively). Among the 4 pediatric patients, 3 have discontinued transfusion shortly after gene therapy and are transfusion independent at the last follow-up (13, 10 and 8 months respectively). One pediatric patient is still receiving regular blood transfusions. A correlation was observed between level of engraftment of gene-marked cells in peripheral blood and bone marrow and transfusion requirement. Preliminary data suggest that the applied clinical protocol for gene therapy with GLOBE LV is well tolerated and leads to significantly reduced transfusion requirement. Follow up analysis are ongoing and updated clinical outcome will be presented.

22. Phase II, multiple-dose study of anti-FcRn Antibody, Rozanolixizumab (UCB7665), in patients with primary immune thrombocytopenia: Interim analysis

Author(s): Robak T.; Jarque I.; Musteata V.; Kiessling P.; Massow U.; Higginson J.; Snipes R.; Jolles S.

Source: Blood; Dec 2017; vol. 130

Publication Type(s): Conference Abstract

Abstract: Introduction Rozanolixizumab is a humanized, high-affinity, anti-human neonatal Fc receptor (FcRn) monoclonal antibody, developed with the aim of reducing levels of pathogenic immunoglobulin G (IgG) in autoimmune and alloimmune diseases. In a first-in-human (FIH) healthy subject trial (NCT02220153), single-dose rozanolixizumab was well tolerated at doses up to 4 mg/kg intravenous (IV) and 7 mg/kg subcutaneous (SC) (Kiessling P et al. P3-48, Peripheral Nerve Society Annual Meeting, Sitges, Spain, 11 July 2017). Severe treatment-emergent adverse events (TEAEs; headache and back pain) occurred with 7mg/kg IV. No severe TEAEs were reported with SC administration. IgG concentrations were reduced by up to 48%, with the greatest mean reduction at maximum dose reached by Day 10, returning to baseline by Day 57. Here we report an interim analysis (5th Data Monitoring Committee review) of an ongoing Phase II, open-label study evaluating the safety, tolerability and efficacy of rozanolixizumab in patients (pts) with primary persistent or chronic immune thrombocytopenia (ITP) (NCT02718716). Methods Eligibility criteria included: >=18 years of age, diagnosis of primary ITP for a minimum of 3 months prior to screening, platelet count <30x10 /L at screening and <35x109/L at baseline, current or history of a peripheral blood smear consistent with ITP. Eligible pts received weekly doses of SC rozanolixizumab (5x4 mg/kg), following a review of pt responses, the weekly dose was escalated (3x7 mg/kg). The primary objective is to evaluate the safety and tolerability of rozanolixizumab. Interim analysis data cut-off: 21 February 2017. Results A total of 28 pts received rozanolixizumab: 4 mg/kg (n=15), 7 mg/kg (n=13). Median age was 56.0 years (range 20-86); 4 mg/kg 66.0 (21-86) and 7 mg/kg 54.0 (20-73). Median duration of disease at baseline was 5.6 years; 4 mg/kg 7.1 and 7 mg/kg 3.8. Of 26 pts who received prior ITP therapies, median number of therapies was 4.0 (range 1-15); 4 mg/kg 4.0 (1-15; n=14) and 7 mg/kg 3.5 (1-12; n=12). Most common therapies (by preferred term): azathioprine (12/28 patients, 42.9%; 4 mg/kg 46.7% and 7 mg/kg 38.5%), romiplostim (11/28, 39.3%; 4 mg/kg 46.7% and 7 mg/kg 30.8%), immunoglobulins (10/28, 35.7%; 4 mg/kg 33.3% and 7 mg/kg 38.5%). Overall, 18/28 (64.3%) pts reported at least 1 TEAE (combined total of 55 TEAEs); 12/15 (80.0%) pts in the 4 mg/kg group and

6/13 (46.2%) pts in the 7 mg/kg group. Apart from 1 severe (Common Terminology Criteria for Adverse Events [CTCAE] Grade 3 or above) TEAE (bleeding from genital tract) in the 4 mg/kg group, deemed unrelated to study medication by the investigator, all TEAEs reported were mild/moderate (CTCAE Grade 1/2). One pt reported a TEAE deemed related to study medication by the investigator: CTCAE Grade 1 injection site reaction in the 4 mg/kg group, which did not interfere with subsequent dosing. The most frequently reported TEAE was headache (CTCAE Grade 1): 3/15 (20.0%) pts in 4 mg/kg group and 4/13 (30.8%) pts in 7 mg/kg group (Table 1). Anti-drug antibodies were detected in 19/28 pts with no effects on rozanolixizumab pharmacodynamics; 3 cases considered treatment emergent. No clinically relevant changes were observed in all other hematology, coagulation, clinical chemistry (including albumin), urinalysis, ECGs, vital signs or liver function tests. No opportunistic infections were reported. No treatment discontinuations due to TEAEs or TEAEs leading to death were reported. At the interim analysis, maximum mean decreases in total IgG levels were observed at Day 29 for the 4 mg/kg group (43.6%, range 21.9-68.6) and at Day 22 for the 7 mg/kg group (50.5%, 35.7-65.5). Clinically relevant improvement in platelet counts (values >=50x10 /L) were reported for 8 pts (53.3%) in the 4 mg/kg group (maximum value range: 50x10 /L to 198x10 /L) and 4 pts (30.8%) in the 7 mg/kg group (59x10 /L to 133x10 /L). In this population of responders, maximal reductions in IgG levels were observed, ranging from 23.9-68.6% in the 4 mg/kg group and 51.1-65.5% in the 7 mg/kg group. Conclusion From the data available to date, multiple dosing with rozanolixizumab 4 mg/kg SC and 7 mg/kg SC has been well tolerated in pts with ITP, and initial platelet responses have been observed in both dose groups. The safety profile for SC rozanolixizumab reported in this trial is in line with the safety profile reported in the FIH trial with healthy subjects receiving SC rozanolixizumab.

23. Recombinant human thrombopoietin (rhTPO) and high-dose dexamethasone (HD-DXM) versus high-dose dexamethasone monotherapy as frontline treatment in newly diagnosed adult immune thrombocytopenia (ITP): A prospective, multicentre, randomised, controlled trial

Author(s): Wang M.; Qin P.; Zhou H.; Peng J.; Hou M.; Zhou F.; Zhao H.; Wang X.; Xu R.; Li D.; Wang L.; Zhou Y.; Feng Y.; Zhang M.; Yang L.; Zeng Q.; Zhang H.; Sun Z.; Wang J.; Liu G.; Guo X.; Wang Z.; Yu W.; Chu X.; Yuan C.; Bi K.; Wang Y.; Ran X.

Source: Blood; Dec 2017; vol. 130

Publication Type(s): Conference Abstract

Abstract: Introduction: Immune thrombocytopenia (ITP) is an acquired thrombocytopenia and caused by immune-mediated platelet destruction and impaired platelet production. Corticosteroids are recommended as the standard first-line treatment. As the immunosuppressive therapy,HD-DXM could decrease platelet destruction by regulating T cell immune abnormalities. Thrombopoietin (TPO) is the primary regulator of thrombopoiesis. Several studies have proved that TPO have profound effects on megakaryocyte development and platelet production as well as restore immune tolerance. We suppose the rhTPO and HD-DXM could work synergistically based on these mechanisms. Recently, several pilot studies have examined the efficacy and safety of TPO-RA in treatment-naive adult ITP patients. We present the results of the first prospective,multicenter,randomized,controlled trial on the largest cohort to date comparing the efficacy and safety of HD-DXM plus rhTPO vs HD-DXM as frontline therapy in newly diagnosed adult primary ITP patients. Methods: Between July 2013 and December 2016, 245 newly-diagnosed, treatment-naive ITP patients aged 18-75 years in 25 separate centers in China were enrolled in the trial (NCT01734044). DXM was administered orally at 40 mg daily for 4 consecutive days to both arms. The 4-day course of dexamethasone was repeated on days 11 to 14 in the case of lack of response. Patients in the experimental arm received subcutaneously rhTPO at a daily dose of 300U/kg concomitantly during the first 14 days. Patients with platelet counts higher than 100x109/L

or more than 50x109/L increase of the baseline platelet count could discontinue the rhTPO treatments. Use of rescue treatments such as platelet transfusion and hemostatic agents were allowed at the discretion of the investigator if the platelet count <10x109/L or >=10x109/L with active bleeding and were recorded. Patients were assessed at day 14. Study visits were scheduled every 1 month until the end of the 6th month or day of relapse. The primary endpoint was the early response rates at day 14 (OR: platelet count >=30x109/L and at least 2-fold increase of the baseline platelet count and absence of bleeding, CR: platelet count >=100x109/L). Key secondary endpoints were rates of sustain response and complete response at the end of month 6, duration of response (DOR), bleeding scores, assessments of adverse events (AEs). Any administration of additional ITP specific medication or withdrawn from the study because of no response was regarded as nonresponders. Results: 196 patients were randomly to receive HD-DXM with (n=100) or without (n=96) rhTPO. Demographics and baseline characteristics were balanced between the 2 arms. HD-DXM+ rhTPO resulted in a higher incidence of early OR at day 14 compared with HD-DXM monotherapy (89.0% vs 66.7%, P<0.001, table 1), the CR rate were 75.0% (HD-DXM+ rhTPO) vs 42.7% (HD-DXM) (P<0.001). Sustained OR and CR at the end of the 6th month was also higher in patients treated with HD-DXM+ rhTPO than in those treated with HD-DXM alone (OR: 51.0% vs 36.5%, P=0.022; CR: 46.0% vs 32.3%, P=0.043, table 1). Throughout the follow-up period, overall duration of response was greater in the experimental group, estimated by the Kaplan-Meier analysis (Figure 1, P=0.04). There was no difference between these 2 groups in terms of TTR, bleeding scores and rescue treatments. No statistically significant differences were observed in the incidence of treatment-related AEs between the two groups. Three patients had grade 4 or higher AEs in the HD-DXM+ rhTPO group, including early cerebral hemorrhage (n=2) and cerebral infarction (n=1); none were deemed treatment-related, one patient in the rhTPO group died of early cerebral hemorrhage. No patient was tested positive for neutralizing antibodies against TPO. Conclusions: Our findings suggest that the addition of rhTPO to HD-DXM is superior to HD-DXM monotherapy in the treatment of newly diagnosed treatment-naive adult ITP patients. Thus, this combination can be a feasible frontline therapy in adult ITP.

24. Clinical outcomes up to 3 years following lentiglobin gene therapy for transfusion-dependent beta-thalassemia in the northstar Hgb-204 study

Author(s): Kwiatkowski J.L.; Thompson A.A.; Rasko J.; Hongeng S.; Anurathapan U.; Leboulch P.; Schiller G.J.; Cavazzana M.; Ho P.J.; Von Kalle C.; Kletzel M.; Vichinsky E.; Deary B.; Asmal M.; Walters M.C.

Source: Blood; Dec 2017; vol. 130

Publication Type(s): Conference Abstract

Abstract:BACKGROUND: Autologous hematopoietic stem cell (HSC) gene therapy could be an effective treatment for transfusion-dependent beta-thalassemia (TDT) without some of the limitations and risks associated with allogeneic HSC transplantation. LentiGlobin Drug Product (DP) contains autologous HSC (CD34+ cells) transduced ex vivo with the betibeglogene darolentivec (BB305) lentiviral vector encoding a human beta-globin gene with the antisickling T87Q mutation (HbA). The Northstar Study(HGB-204; NCT01745120) is an international, multi-center phase 1/2 clinical trial examining the safety and efficacy of LentiGlobin investigational gene therapy in patients with TDT. As of the most recent data cut (June 2, 2017), all patients have 1 to 3 years of follow-up post DP infusion. METHODS: Patients (12-35 years of age) with TDT were enrolled at participating sites in the U.S., Australia, and Thailand. Autologous CD34+ cells were collected by mobilization and apheresis and transduced with the BB305 vector in a centralized facility. Patients underwent myeloablative conditioning with intravenous busulfan prior to infusion of transduced cells. Patients were monitored for hematologic engraftment, vector copy number (VCN), levels of HbA , and red

blood cell (RBC) transfusion requirements post-infusion. Safety data, including adverse events (AEs), vector integration site analysis, and surveillance for replication competent lentivirus (RCL), were evaluated post-infusion. The primary analysis period for the study is 24 months following infusion; patients then transition into a long-term study for an additional 13 years of follow-up. RESULTS: Eighteen patients with TDT (8 with beta0/beta0and 10 with non-beta0/beta0genotypes; aged 12-35 years) received LentiGlobin DP. The median DP VCN was 0.7 (range: 0.3-1.5) copies/diploid genome, the median cell dose was 8.1 x 106 (range: 5.2-18.1 x 106) CD34+ cells/kg, and the proportion of transduced CD34+ cells was 17-58%. The toxicity profile observed to date has been typical of myeloablative conditioning. During a follow-up period of up to 38.3 months post-infusion (median 25.5 months; range: 14.9-38.3 months), there have been no >= grade 3 DP-related AEs and no evidence of clonal dominance or RCL. Serious AEs occurring after DP infusion have been reported in 6/18 (33%) patients: venoocclusive liver disease (n=2) and 1 case each of cellulitis, diarrhea, gastroenteritis, Klebisella infection, cardiac ventricular thrombosis, device-related thrombosis, and hyperglycemia. No serious AEs were considered related to DP. Of the 10 patients with non-beta0/beta0genotypes, 8 have been free of transfusions for a median of 27.1 (range 12.5-35.2) months. At their latest study visit (n=8: Months 15-36), their total Hb level ranged from 9.3-13.7 g/dL, and their HbA level was 3.6-9.6 g/dL. The peripheral VCN ranged from 0.1-1.0. Notably, of these 8 patients, 6 have achieved "transfusion independence" (TI), defined as >=12 months without transfusions with a weighted average Hb >=9 g/dL. The 2 patients with non-beta0/beta0genotypes who still require intermittent transfusions had annual transfusion volumes reduced by 30% and 94%; both received DP with a VCN in the lower range (DP VCNs: 0.3 and 0.4). Two patients with beta0/beta0genotypes have not received a transfusion in more than a year. At the patients' last study visit (Month 24/Month 12), total Hb levels were 9.0 and 10.2 g/dL, HbA levels were 8.4 and 6.8 g/dL, and peripheral VCNs were 0.9 and 0.6, respectively. Six patients with beta0/beta0genotypes have continued transfusions. However, their annual transfusion volumes have decreased by a median of 63% (range: 19% to 81%), from an annualized volume of 124.4-261.3 ml/kg/year at baseline to an annualized volume of 31.4-212.6 ml/kg/year (from 6 months post-infusion to data cut). CONCLUSIONS: With up to 3 years of follow-up, the Northstar Study is the largest international gene therapy trial in TDT to date. All patients, 9 of whom have at least 2 years of follow-up, have demonstrated ongoing clinical benefit with a manageable safety profile. A total of 10 patients (8/10 with non-beta0/beta0, 2/10 with beta0/beta0genotypes) have been able to discontinue RBC transfusions and remain clinically well. The 8/18 patients still receiving transfusions have significantly reduced annualized transfusion volumes (up to 81% and 94% in patients with beta0/beta0and non-beta0/beta0genotypes, respectively).

25. Hydroxyurea for hemoglobin E/beta-thalassemia: a systematic review and meta-analysis

Author(s): Algiraigri A.H.; Kassam A.

Source: International Journal of Hematology; Dec 2017; vol. 106 (no. 6); p. 748-756

Publication Type(s): Article

Abstract: Hemoglobin E-beta thalassemia (Hb E/beta-thalassemia) is a distinct, yet common, type of beta-thalassemia, in which the patient co-inherits a beta-thalassemia allele from one parent, and a structural variant, Hb E, from the other parent. This co-inheritance leads to remarkable clinical heterogeneity, varying degrees of chronic anemia, and a wide spectrum of complications due to ineffective erythropoiesis and iron overload. Hydroxyurea (HU), an oral chemotherapeutic drug, is expected to decrease disease severity. To assess the clinical efficacy and safety of HU in Hb E/beta-thalassemia patients. We searched MEDLINE, EMBASE, Cochrane databases, and major preceding conferences for studies that assessed HU in Hb E/beta-thalassemias patients. The effect size was estimated as a proportion (responder/sample size). Qualities of eligible studies were assessed using

NIH tools. A total of five [one randomized clinical trial (RCT) and four observational] studies involving 106 patients were included. HU was associated with a significant RR of 46% with no statistical heterogeneity. No serious adverse effects were reported. Patients with Hb E/beta-thalassemia may benefit from a trial of HU, though large RCTs assessing efficacy should be conducted to confirm the findings of this meta-analysis and to assess long-term toxicity and response sustainability.

26. New therapeutic targets in transfusion-dependent and -independent thalassemia

Author(s): Cappellini M.D.; Motta I.

Source: Hematology; Dec 2017; vol. 2017 (no. 1); p. 278-283

Publication Type(s): Article

Abstract:beta-Thalassemias are characterized by reduced production of beta-globin chain, resulting in a/b-chain unbalance and precipitation of alpha-globin-heme complexes and determining ineffective erythropoiesis. Ineffective erythropoiesis, chronic hemolytic anemia, and compensatory hematopoietic expansion are the disease hallmarks, and they are related to the severity of the chain unbalance. Several clinical forms of beta-thalassemia, including the coinheritance of beta-thalassemia with hemoglobin E resulting in hemoglobin E/beta-thalassemia, have been described. Clinically, beta-thalassemias can be classified as transfusion-dependent thalassemia (TDT) and non-transfusion-dependent thalassemia (NTDT) according to the severity of the phenotype, which is caused by a wide spectrum of mutations in a homozygous or compound heterozygous state. Current treatment of TDT consists of regular transfusions that lead to iron overload, requiring iron chelation to prevent iron-related organ toxicity. NTDT patients do not require transfusions or only occasionally require them; however, they develop iron overload as well because of increased intestinal iron absorption caused by chronic anemia. Hematopoietic stem cell allogenic transplant is the only approved cure for b-thalassemia; however, it is still limited by clinical conditions and the availability of matched donors as well as by potential graft-versus-host disease (GVHD). Gene therapy could avoid the GVHD risk, although hematopoietic stem cells must be genetically modified ex vivo. Epigenetic manipulation and genomic editing are novel experimental approaches. An increased understanding of the pathophysiology that controls the disease process prompted us to explore alternative therapeutic approaches that address the underlying chain unbalance, ineffective erythropoiesis, and iron dysregulation. Molecules, such as JAK2 inhibitors and the activin-receptor ligand trap that target ineffective erythropoiesis, are already in clinical trials with promising results. Other agents aimed to generate iron-restricted erythropoiesis are also under experimental evaluation.

27. Intravenous iron vs blood for acute post-partum anaemia (IIBAPPA): a prospective randomised trial.

Author(s): Chua, Seng; Gupta, Sarika; Curnow, Jennifer; Gidaszewski, Beata; Khajehei, Marjan; Diplock, Hayley

Source: BMC pregnancy and childbirth; Dec 2017; vol. 17 (no. 1); p. 424

Publication Type(s): Journal Article

Available at BMC pregnancy and childbirth - from BioMed Central

Available at BMC pregnancy and childbirth - from Europe PubMed Central - Open Access

Available at BMC pregnancy and childbirth - from nih.gov

Abstract:BACKGROUNDAcute post-partum anaemia can be associated with significant morbidity including a predisposition for postnatal depression. Lack of clear practice guidelines means a number

of women are treated with multiple blood transfusions. Intravenous iron has the potential to limit the need for multiple blood transfusions but its role in the post-partum setting is unclear.METHODS/DESIGNIIBAPPA is a multi-centre randomised non-inferiority trial. Women with a primary post-partum haemorrhage (PPH) >1000 mL and resultant haemoglobin (Hb) 5.5-8.0 g/dL after resuscitation with ongoing symptomatic anaemia who are otherwise stable (no active bleeding) are eligible to participate. Patients with sepsis or conditions necessitating rapid Hb restoration are excluded. Eligible participants are randomised to receive a blood transfusion or a single dose of intravenous iron polymaltose calculated using the Ganzoni formula. Primary outcome measures include Hb, Ferritin and C-Reactive Protein levels on Day 7. Secondary outcomes evaluate (i) Hb, Ferritin and CRP levels on Day 14, 28, (ii) anaemia symptoms on Day 0, 7, 14 and 28 using structured health related quality of life questionnaires, (iii) treatment safety by assessing adverse reactions and infection endpoints and (iv) the quantitative impact of anaemia on breast feeding quality using a hospital designed questionnaire.DISCUSSIONIf equivalence in Hb and ferritin levels, symptom scores and safety endpoints is demonstrated, intravenous iron may become the preferred treatment for women with acute post-partum anaemia to minimise transfusion reactions and costs.TRIAL REGISTRATIONAustralian and New Zealand Clinical Trials Registry: ACTRN12615001370594 on 16th December, 2015 (prospective approval).

28. Constructing a core outcome set for immune thrombocytopenia in pregnancy

Author(s): Malinowski A.K.; Shehata N.; D'Souza R.

Source: Journal of Evidence-Based Medicine; Nov 2017; vol. 10 ; p. 38

Publication Type(s): Conference Abstract

Abstract: Immune thrombocytopenia (ITP) is a clinical syndrome characterized by a low platelet count and increased risk of bleeding. It frequently occurs in women of childbearing age and affects ~1 to 10/10,000 pregnancies. In pregnancy, platelet antibodies can cross the placenta resulting in neonatal thrombocytopenia. Current literature contains studies that vary in regard to the reported outcomes and theirmeasurement; limiting the ability to undertake rigorous meta-analysis that would enable extracting stronger conclusions, bolstered by larger sample sizes. The objective of this project is to generate a core outcome set for studies focusing on the evolution and management of ITP in pregnancy. A systematic review (SR) of randomized control trials and cohort studies will be completed to identify all reported outcomes, their definitions, and measurements. More specifically, the SR will aim to determine what maternal and fetal/neonatal outcomes (laboratory, radiologic, and clinical) have been explored in studies of ITP, how these were measured (ie, evaluation of bleeding events, etc.), and for what type of intervention (ie, IVIg, corticosteroids, other). Key stakeholders including experts in the field (ie, obstetricians, maternal-fetal medicine specialists, hematologists, obstetric medicine physicians, nurses, neonatologists, and researchers), and healthcare users will be identified and their input will be sought with respect to the composition of the COS for ITP in pregnancy and postpartum. Utilizing the Delphi technique, the results gathered in this manner will be collated and re-presented to the stakeholders alongside outcomes identified through the systematic reviewfor round 2.At each round of this iterative process, participants will be provided with the analysis of the responses of that round and via pre-determined criteriawill be able to add further outcomes or change the importance of the ones they previously identified. Criteria for consensus will be clearly defined a priori.

29. Life-threatening bleeding episodes in primary immune thrombocytopenia: a single-center retrospective study of 169 inpatients

Author(s): Tsuda H.; Tsuji T.; Yamasaki H.; Tsuji M.

Source: Annals of Hematology; Nov 2017; vol. 96 (no. 11); p. 1915-1920

Publication Type(s): Article

Abstract: Bleeding is the most important clinical outcome in patients with immune thrombocytopenia (ITP), and the goal of therapy in such cases is to treat or prevent bleeding. The frequency of and risk factors for bleeding events in ITP have only recently been identified in several large-scale studies. However, there is little published information about severe life-threatening bleeding in ITP. To clarify the clinical features of life-threatening bleeding in patients with primary ITP, we systematically reviewed the medical records of all ITP patients that were admitted to our hospital between January 1, 1992, and December 31, 2015. Of 169 consecutive inpatients with primary ITP, 8 suffered life-threatening bleeding (10 episodes: gastrointestinal, 4 cases; pulmonary, 1 case; and intracranial, 5 cases). All of these patients were >= 60 years of age and had platelet counts of < 20 x 109/L. The highest incidence of such bleeding was found among elderly patients in their 80s with platelet counts of < 5 x 109/L. Among the patients aged >= 60 years with platelet counts of < 20 x 109/L, the background data of the patients with and without life-threatening bleeding episodes were compared. It was shown that the patients in the bleeding group were older than those in the non-bleeding group (80.13 +/- 2.31 vs. 73.39 +/- 2.51 years, p = 0.0266). Hypertension, diabetes mellitus, anticoagulant use, ITP phase, and sex were not identified as strong risk factors for life-threatening bleeding. Combining age and the platelet count might be a useful way of identifying ITP patients that are at risk of life-threatening bleeding. Most intracranial hemorrhaging (4/5) was spontaneous and multifocal, suggesting that these might be characteristics of ITP-related bleeding in elderly patients.

30. Tolerability and Efficacy of Eltrombopag in Chronic Immune Thrombocytopenia: Meta-Analysis of Randomized Controlled Trials

Author(s): Elgebaly A.S.; Menshawy A.; Ashal G.E.; Elfil M.

Source: Clinical and Applied Thrombosis/Hemostasis; Nov 2017; vol. 23 (no. 8); p. 928-937

Publication Type(s): Review

Abstract: Background: Eltrombopag is an oral thrombopoietin receptor agonist that stimulates the production of normally functioning platelets. The aim of this meta-analysis is to synthesize evidence about the safety and efficacy of eltrombopag for both adult and children with primary immune thrombocytopenia (ITP). Methods: A computer literature search of PubMed, Scopus, Web of Science, and Cochrane Central was conducted. Records were screened for eligible studies, and data were extracted and synthesized using Review Manager for Windows. Subgroup analysis and sensitivity analysis were conducted to investigate whether treatment effect varies significantly between adults and children. Results: Six randomized controlled trials (N = 611 patients) were included in the final analysis. The overall effect estimates favored eltrombopag group in terms of overall platelet response (relative risk [RR]: 3.42; 95% confidence interval [CI]: 2.51-4.65; P <.0001), incidence of significant bleeding (RR: 0.56; 95% CI: 0.41-0.77; P =.0004), and number of cases needed to rescue treatment (RR: 0.45; 95% CI: 0.32-0.65; P <.0001). The efficacy of eltrombopag did not differ significantly between children and adults except for incidence of any bleeding (RR: 0.83 vs 0.51; P =.008). Conclusion: Eltrombopag is a tolerable and effective drug for the management of chronic ITP in children and adults.

31. Is there a standard-of-care for transfusion therapy in thalassemia?

Author(s): Franchini M.; Liumbruno G.M.; Forni G.L.

Source: Current Opinion in Hematology; Nov 2017; vol. 24 (no. 6); p. 558-564

Publication Type(s): Review

Abstract: Purpose of review Thalassemia is the most common form of inherited anemia, characterized by variable clinical phenotypes. The purpose of this review is to summarize the transfusion support in thalassemia patients and the management of transfusion-related iron overload. Recent findings The most recent evidence on transfusion strategy and iron chelation therapy in thalassemia arising from clinical trials as well as from recommendation guidelines are critically discussed. Summary Enhancements in the global care of thalassemia, resulting from the combination of an appropriate transfusion approach and iron chelation therapy, have produced a significant improvement in the quality of life and, finally, in the prognosis of patients affected by this inherited hematologic disorder.

32. Misdiagnosis of primary immune thrombocytopenia and frequency of bleeding: lessons from the McMaster ITP Registry.

Author(s): Arnold, Donald M; Nazy, Ishac; Clare, Rumi; Jaffer, Anushka M; Aubie, Brandon; Li, Na; Kelton, John G

Source: Blood advances; Nov 2017; vol. 1 (no. 25); p. 2414-2420

Publication Type(s): Journal Article

Available at Blood advances - from nih.gov

Abstract: Nonspecific diagnostic criteria and uncertain estimates of severe bleeding events are fundamental gaps in knowledge of primary immune thrombocytopenia (ITP). To address these issues, we created the McMaster ITP Registry. In this report, we describe the methodology of the registry, the process for arriving at the diagnosis, and the frequency of bleeding. Consecutive patients with platelets 1 visit was 1.7 years (interquartile range, 0.8-3.4). At registration, 295 patients were initially diagnosed with primary ITP; of those, 36 (12.2%) were reclassified as having a different diagnosis during follow-up. At registration, 319 patients were initially diagnosed with another thrombocytopenic condition; of those, 10 (3.1%) were ultimately reclassified as having primary ITP. Of 269 patients with a final diagnosis of primary ITP, 56.5% (95% confidence interval [CI], 50.4-62.5] experienced grade 2 bleeding at 1 or more anatomical site, and 2.2% (95% CI, 0.8-4.8) had intracranial hemorrhage. Nearly 1 in 7 patients with primary ITP were misdiagnosed. Grade 2 bleeding was common. Registry data can help improve the clinical and laboratory classification of patients with ITP.

33. Evaluation of OSMOCELLS, a new semi-automatic device for osmotic fragility assessment.

Author(s): Gérard, D; Fattet, A-J; Brakta, C; Phulpin, A; Steschenko, D; Lesesve, J-F; Perrin, J

Source: International journal of laboratory hematology; Oct 2017; vol. 39 (no. 5); p. 521-527

Publication Type(s): Journal Article

Abstract:INTRODUCTIONThe osmotic fragility (OF) test was a central test for the diagnosis of hereditary red blood cell (RBC) disorders (mostly hereditary spherocytosis (HS), but thalassaemia as well). Nowadays although the traditional multitubes method has lost a prominent place, many laboratories still perform such a laboured test, despite the lack of standardization. In fact, the evaluation of OF may offer an inexpensive screening for RBC disorders. We present a new semi-automatic device, allowing the continuous recording of OF, by an updated dialysis method.METHODSRepeatability, stability over time, influence of the anticoagulant were evaluated among a population of healthy blood donors. The test was then performed among patients presenting inherited RBC disorders (HS or haemoglobinopathies) where OF is typically

altered.RESULTSRepeatability was excellent; the parameters were greatly influenced by the nature of the anticoagulant and interestingly appeared stable for 48 h. Patients with RBC disorders displayed the expected profile in regard with their disease: patients with HS all presented an increased OF while patients with haemoglobinopathy displayed resistant profiles.CONCLUSIONThe device offers a substantial improvement in terms of standardization and consistency of the results and may offer a considerable gain for general laboratories.

34. Thrombopoietin-receptor agonists for children with immune thrombocytopenia: a systematic review

Author(s): Zhang J.; Li Y.; Xie J.; Liang Y.; Ai Y.; Zheng W.

Source: Expert Opinion on Pharmacotherapy; Oct 2017; vol. 18 (no. 15); p. 1543-1551

Publication Type(s): Review

Abstract: Objective: We conducted a systematic review to assess the efficacy and safety of Thrombopoietin-receptor agonists (TPOras) for pediatric immune thrombocytopenia (ITP). Methods: We searched PubMed, Embase and Cochrane Library from their earliest records to January 2017. Randomized controlled trials (RCTs) were included. Primary outcomes were durable response and clinically significant bleeding. Secondary outcomes were overall response, overall bleeding events, the use of rescue medication and adverse events (AEs). Results: Five randomized RCTs (261participants) were included. Compared with placebo group, the proportion of patients achieving durable platelet response was significantly higher in Eltrombopag (P = 0.0004) or Romiplostim (P = 0.002) group, so was the overall response in Eltrombopag [RR = 2.64, 95% CI (1.58, 4.44)] or Romiplostim [RR = 5.05, 95% CI (2.21, 11.53)] group. Both clinically significant bleeding (P = 0.04) and total bleeding (P = 0.01) in Eltrombopag group were significantly less frequent than those in placebo group, while no significant difference between Romiplostim and placebo group. The proportion of patients receiving rescue medication, the incidence of overall AEs and serious AEs between TPO-receptor agonists and placebo group were not significantly different. Conclusion: TPOras might improve both durable and overall platelet response in pediatric ITP, compared with placebo.

35. Improving transfusion practice in transfusion dependent thalassaemia patients

Author(s): Wickremaarachchi C.; McGill E.; Bosco A.; Kidson-Gerber G.

Source: Thalassemia Reports; Oct 2017; vol. 7 (no. 1); p. 30-31

Publication Type(s): Article

Available at Thalassemia Reports - from pagepressjournals.org

Abstract: The aim of this study was to improve current transfusion practice in transfusiondependent thalassaemia patients by determining whether safe transition from triplewashed red cells (TWRC) to leucodepleted red cells (LDRC), increasing transfusion rates, reducing the use of frusemide and creating uniform practice across patients is possible. In patients receiving regular transfusions (50), triple-washed red blood cells were changed to LDRC, transfusion rates were increased to 5 mL/kg/h (in line with the Cooley's Foundation guidelines) to a maximum of 300 mL/h and frusemide was ceased. Medical review occurred at completion of the transfusion. Of the 20 patients on TWRC, 18 were transitioned to leucodepleted red cells (90%). Recurrent allergic reactions in 2 patients required re-institution of TWRC. 7 of the 8 patients on regular frusemide ceased this practice with no documented transfusion-related fluid overload. One patient refused. Of the eligible 50 patients, 20 patients (40%) were increased to the maximum transfusion rate of 300 mLs/h; 6 (12%) increased rate but refused to go to the maximum; 9 (18%) refused a change in practice and 15 (30%) were

already at the maximum rate. There was only one documented transfusion reaction (palpitations) however this patient was able to tolerate a higher transfusion rate on subsequent transfusions. Thalassemia patients on TWRC were safely transitioned to LDRC. Transfusion rates were safely increased, with a calculated reduction in day-stay bed time of 17.45 h per month. This confirms a guideline of 5 mL/kg/h for transfusion-dependant thalassaemia patients with preserved cardiac function is well tolerated and may be translated to other centres worldwide.

36. Tolerability and safety of the intravenous immunoglobulin octagam 10% in patients with immune thrombocytopenia: a post-authorisation safety analysis of two non-interventional phase IV trials

Author(s): Wietek S.; Svorc D.; Debes A.; Svae T.-E.

Source: Hematology; Oct 2017 ; p. 1-6

Publication Type(s): Article In Press

Available at Hematology - from EBSCO (MEDLINE Complete)

Abstract: Objectives: To provide detailed data on the tolerability and safety of octagam 10%, a ready-to-use intravenous immunoglobulin, in a subgroup of patients with immune thrombocytopenia (ITP) involved in an integrated analysis of post-authorisation safety surveillance (PASS) studies. Methods: A subgroup analysis was conducted using data collected from two non-interventional studies that included patients with ITP treated with octagam 10%. Patients were observed and monitored for possible adverse drug reactions (ADRs) during or after administration of octagam 10%, with a particular focus on thromboembolic events (TEEs). ADRs were analysed at the case and event level. Results: In this analysis of 112 patients receiving octagam 10% (mean dose 0.4 g/kg/infusion), there were five cases with at least one adverse drug reaction (ADR) associated with 626 infusions of octagam 10% (case incidence of 0.8% per infusion). ADRs were of mild or moderate severity. There were a total of 10 events, most commonly back pain (n=3) and headache (n=2). Nausea, dizziness and a sensation of heaviness were also reported. The remaining two events involved drug exposure during pregnancy. There were no TEEs or other serious ADRs. Discussion: In this subgroup analysis of patients who received octagam 10% (manufactured using an amended process) in two PASS studies, the overall ADR rate was low, with ADRs occurring in only 0.8% of all infusions. No TEEs or other serious ADRs were reported. Conclusions: Routine clinical use of octagam 10% was safe and well tolerated, with no unexpected safety issues, in patients with ITP. The two studies from which data were taken are registered with the International Standard Randomised Controlled Trial Number Registry, numbers ISRCTN58800347 and ISRCTN02245668.

37. Retrospective review of effectiveness and safety of intravenous ferric carboxymaltose given to children with iron deficiency anaemia in one UK tertiary centre

Author(s): Tan M.L.N.; Windscheif P.-M.; Thornton G.; Gaynor E.; Rodrigues A.; Howarth L.

Source: European Journal of Pediatrics; Oct 2017; vol. 176 (no. 10); p. 1419-1423

Publication Type(s): Review

Abstract: In the paediatric population, ferric carboxymaltose (FCM) is only licenced for use in children older than 14 years, and the data in younger children remains scarce. We retrospectively reviewed data of all paediatric patients less than 14 years old who had received FCM infusion from August 2011 to June 2015 at the John Radcliffe Hospital (Oxford University Hospitals), UK. The patient demographics, significant medical history, FCM dose, and blood investigations (pre-FCM and post-FCM) were reviewed. Of the 51 children, 41 had inflammatory bowel disease. There were 24 girls

and 27 boys, aged 1 to 13 years, mean (SD) weight 28.4 (13.6) kg. Fifteen patients received at least one more course of FCM up to 35 months later. The time interval between pre-FCM and post-FCM investigations was 1 to 8 months. An improved, median (range) rise in blood indices following one FCM infusion was haemoglobin 2.7 (- 2.4 to 7) g/dL, serum iron 6.6 (- 0.6 to 21.1) mumol/L, and transferrin saturation 14 (- 14 to 38)%. No adverse outcomes were documented. Conclusions: FCM was effective in increasing the key blood indices with no adverse outcomes in children less than 14 years of age, with a range of different conditions, majority with gastrointestinal disorders such as IBD.

38. Tolerability and safety of the intravenous immunoglobulin octagam® 10% in patients with immune thrombocytopenia: a post-authorisation safety analysis of two non-interventional phase IV trials.

Author(s): Wietek, Stefan; Svorc, Daniel; Debes, Anette; Svae, Tor-Einar

Source: Hematology (Amsterdam, Netherlands); Oct 2017 ; p. 1-6

Publication Type(s): Journal Article

Available at Hematology (Amsterdam, Netherlands) - from EBSCO (MEDLINE Complete)

Abstract:OBJECTIVESTo provide detailed data on the tolerability and safety of octagam® 10%, a ready-to-use intravenous immunoglobulin, in a subgroup of patients with immune thrombocytopenia (ITP) involved in an integrated analysis of post-authorisation safety surveillance (PASS) studies.METHODSA subgroup analysis was conducted using data collected from two non-interventional studies that included patients with ITP treated with octagam® 10%. Patients were observed and monitored for possible adverse drug reactions (ADRs) during or after administration of octagam® 10%, with a particular focus on thromboembolic events (TEEs). ADRs were analysed at the case and event level.RESULTSIn this analysis of 112 patients receiving octagam® 10% (mean dose 0.4 g/kg/infusion), there were five cases with at least one adverse drug reaction (ADR) associated with 626 infusions of octagam® 10% (case incidence of 0.8% per infusion). ADRs were of mild or moderate severity. There were a total of 10 events, most commonly back pain (n = 3) and headache (n = 2). Nausea, dizziness and a sensation of heaviness were also reported. The remaining two events involved drug exposure during pregnancy. There were no TEEs or other serious ADRs.DISCUSSIONIn this subgroup analysis of patients who received octagam® 10% (manufactured using an amended process) in two PASS studies, the overall ADR rate was low, with ADRs occurring in only 0.8% of all infusions. No TEEs or other serious ADRs were reported.CONCLUSIONSRoutine clinical use of octagam® 10% was safe and well tolerated, with no unexpected safety issues, in patients with ITP. The two studies from which data were taken are registered with the International Standard Randomised Controlled Trial Number Registry, numbers ISRCTN58800347 and ISRCTN02245668.

39. Using a standardised protocol was effective in reducing hospitalisation and treatment use in children with newly diagnosed immune thrombocytopenia.

Author(s): Labrosse, R; Vincent, M; Nguyen, U-P; Chartrand, C; Di Liddo, L; Pastore, Y

Source: Acta paediatrica (Oslo, Norway : 1992); Oct 2017; vol. 106 (no. 10); p. 1617-1623

Publication Type(s): Journal Article

Abstract:AIMChildhood immune thrombocytopenia (ITP) has been associated with low bleeding rates and a high frequency of spontaneous remission. Although current guidelines suggest that most patients are just observed, children still receive platelet-enhancing therapies for fear of bleeding complications. We hypothesised that a standardised protocol with a step-down approach would

reduce hospitalisation and treatment use.METHODA retrospective chart review was performed on patients diagnosed with acute ITP between January 2010 and December 2014, before (n = 54) and after (n = 37) the standardised protocol, which was introduced in January 2013. Management and events during the first 3 months following diagnosis were recorded.RESULTSThe protocol resulted in a 34% decrease in the hospitalisation rate ($p < 0.001$) at diagnosis. Prednisone treatment duration at diagnosis was also significantly reduced (13.1 versus 5.8 days, $p = 0.004$). Children over 3 years of age were 3.8 times less likely to be hospitalised (95% CI 1.94-7.61) and 2.3 times less likely to receive treatment (95% CI 1.2-4.3). There was no difference in the rate of persistent ITP (38% versus 30%, $p = 0.43$) or serious bleeding complications (7% versus 5%, $p = 0.70$).CONCLUSIONOur ITP management protocol significantly reduced hospitalisation rates and length of prednisone treatment without any increase in disease complications.

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Upcoming events:

South West Lymphoma Group meeting 7/3/2018, Taunton; https://hartleytaylor.co.uk/SWL4/

Recent department publications:

Cancer Patient Experience in the Teenage Young Adult Population- Key Issues and Trends Over Time: An Analysis of the United Kingdom National Cancer Patient Experience Surveys 2010-2014.
Furness CL, Smith L, Morris E, Brocklehurst C, Daly S, Hough RE.
J Adolesc Young Adult Oncol. 2017 Sep;6(3):450-458. doi: 10.1089/jayao.2016.0058. Epub 2017 May 19. PMID:28525286

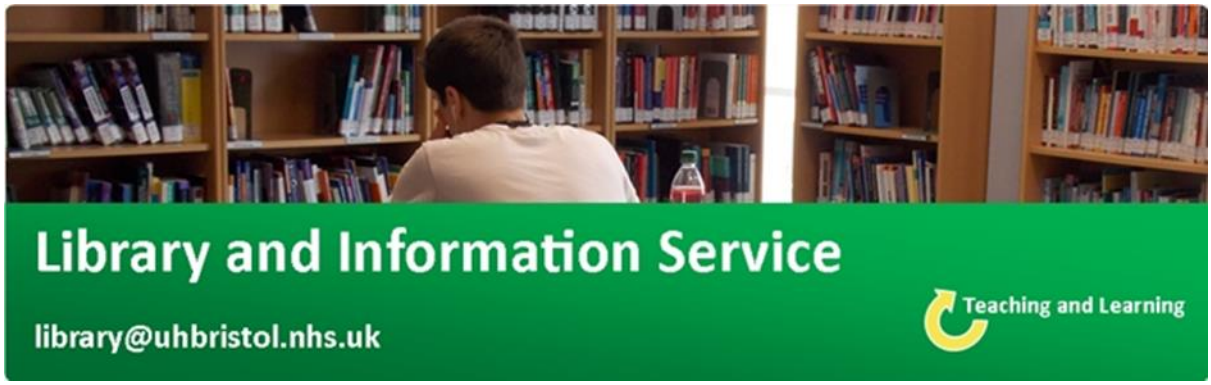
BSH Guideline: management of thrombotic and haemostatic issues in paediatric malignancy.
Sibson KR, Biss TT, **Furness CL**, Grainger JD, Hough RE, Macartney C, Payne JH, Chalmers EA; British Society for Haematology.
Br J Haematol. 2018 Jan 31. doi: 10.1111/bjh.15112. [Epub ahead of print] No abstract available.

Long-term survival following post-allograft relapse of T-cell acute lymphoblastic leukaemia: a novel approach using nelarabine and donor lymphocyte infusions.
Burley K, Wolf J, Raffoux E, Marks DI.
Bone Marrow Transplant. 2017 Dec 21. doi: 10.1038/s41409-017-0038-8. [Epub ahead of print] No abstract available. PMID:29269798

Alemtuzumab-based therapy for Secondary Malignant Histiocytosis arising from Pre-B-ALL.
Abid MB, Wadera K, Bird JM, Pawade J, Marks DI.
Leuk Res Rep. 2017 Dec 5;9:5-8. doi: 10.1016/j.lrr.2017.11.003. eCollection 2018.
PMID:29264111 **Free PMC Article**

Post-allograft relapse of ALL: rational use of the new targeted therapies.
Furness CL, Marks DI.
Curr Med Res Opin. 2017 Dec 1:1-5. doi: 10.1080/03007995.2017.1412946. [Epub ahead of print] No abstract available. PMID:2919548

Who Should Receive a Transplant for Acute Lymphoblastic Leukaemia?
Dhawan R, Marks DI.
Curr Hematol Malig Rep. 2017 Apr;12(2):143-152. doi: 10.1007/s11899-017-0371-4. Review.
PMID:28215040



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