9th Annual Sickle Cell and Thalassaemia Advanced Conference

7-9 October 2015
Welcome
From the course director
Dear colleague

Welcome to the 9th Annual Sickle Cell and Thalassaemia Advanced Conference. It is a great pleasure to welcome you to London on this occasion for interaction between the world’s leading experts in haemoglobinopathies; professionals delivering excellent care to our communities and policy-makers.

The overall aim is to make a difference in the lives of our patients and give them hope by changing the outcome of their disease through evidenced practice.

We hope to achieve this by bringing you all together to discuss the latest evidence of the complications of sickle cell and thalassaemia and how this is being translated into interventions that can make a difference.

We hope to achieve this with lectures, debates and consensus sessions on key management issues, including poster sessions and abstracts.

Key themes for the 2015 conference will include

- Latest developments in the diagnosis and treatment of SCD and thalassaemia
- Improving the quality of life for patients and families affected by SCD and thalassaemia
- The management of SCD in developing and developed countries

Kind regards,

Dr Baba Inusa | Course Director
Lead Consultant Sickle Cell and Thalassaemia Service
Evelina London Children’s Hospital
Guy’s and St Thomas’ NHS Foundation Trust
Senior Lecturer, King’s College
Programme

Day 1

7 October 2015
<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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<tr>
<td>08:00 – 09:00</td>
<td>Registration and Coffee</td>
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<td>09:00 – 10:40</td>
<td><strong>Welcome – Dr Eugene Oteng-Ntim; Guy’s and St Thomas’ NHS Trust (Chair)</strong></td>
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<td></td>
<td>Overview of Sickle Cell Disease and treatment options</td>
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<td><strong>Dr Baba Inusa; Evelina, Guy’s and St Thomas’ NHS Trust, London</strong></td>
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<td></td>
<td>Pathology of Sickle Cell Disease</td>
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<td></td>
<td><strong>Professor Sebastian Lucas; King’s College London</strong></td>
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<td>Assessment and management of iron overload in β- thalassaemia major patients during the</td>
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<td>21st century: a real-life experience from the Italian WEBTHAL project.</td>
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<td><strong>Professor Antonio Piga; School of Medicine, S. Luigi Gonzaga site University of Torino, Italy</strong></td>
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<td>10:40 – 11:00</td>
<td>Coffee Break</td>
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<td>11:00 – 13:00</td>
<td><strong>Parallel Session A – Determinants of Sickle Cell Disease Severity – Chair Dr David Rees</strong></td>
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<td>Association between variants at BCL11A erythroid-specific enhancer and foetal</td>
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<td>haemoglobin levels among Sickle Cell Disease Patients in Cameroon: implications for future</td>
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<td>therapeutic interventions</td>
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<td>**Ambroise Wonkam; Division of Human Genetics, Faculty of Health Sciences, University of</td>
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<td>Cape Town, Cape Town, Republic of South Africa</td>
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<td>Environmental determinants of severity</td>
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<td>**Professor David Rees; Paediatric Haematology, King’s College Hospital, King’s College</td>
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<td>London</td>
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<td>Genetic determinants of severity</td>
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<td><strong>Dr Stephan Menzel; Molecular Genetics, King’s College London</strong></td>
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<td>Biomarkers of severity</td>
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<td><strong>Dr Valentine Brousse; Hôtel universitaire Necker-Enfants Maladies, France</strong></td>
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<td>11:00 – 13:00</td>
<td><strong>Parallel session B – Laboratory Diagnosis – Chair Dr Rachel Kesse-Adu,</strong></td>
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<td><strong>Evelina, Guy’s and St Thomas’ NHS Trust London</strong></td>
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<td>Morphology cases (Quiz)</td>
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<td><strong>Dr Vishal Jayakar; St George’s London</strong></td>
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<td>Haemoglobin switching</td>
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<td><strong>Dr Noémi Roy; – University of Oxford;</strong></td>
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<td>Laboratory Diagnosis of haemoglobinopathy with HPLC examples</td>
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<td><strong>Dr Yvonne Daniel; Viapath Guy’s Hospital, London</strong></td>
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<td>Molecular diagnostics in haemoglobinopathy</td>
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<td><strong>Dr Mary Petrou; Department of Haematology; University College Hospital, London</strong></td>
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<tr>
<td>13:00 – 14:00</td>
<td>Lunch and Meet the Expert</td>
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<td>The management of Thalassaemia in Europe</td>
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<td><strong>Professor Antonio Piga</strong></td>
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<td>Vitamin D in Sickle Cell Disease – when to treat</td>
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<td><strong>Professor David Rees</strong></td>
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<td>Meet the bone marrow transplant co-ordinator</td>
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<td><strong>Mrs Yvonne Harrington</strong></td>
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<td>14:00 – 15:40</td>
<td>USA NIH Clinical Excellence Research Centres – Chair Dr Andrew Campbell</td>
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<td>Evaluation of Severity of Painful Sickle Cell Crises with oral PGLG Treatment <strong>Charles Stark</strong>; Senior Vice President, Research and Development, Emmaus Life Sciences –</td>
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<td>The Cardiomyopathy of Sickle Cell Disease</td>
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<td><strong>Associate Professor Charles Quinn</strong>; Cincinnati Children's Hospital</td>
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<td>Molecular Mechanisms of Pain in Sickle Cell Disease</td>
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<td><strong>Professor Kalpna Gupta</strong>; University of Minnesota Medical School</td>
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<td>Novel Insights into the Pathogenesis of Acute Chest Syndrome</td>
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<td><strong>Associate Professor Solomon Ofori-Acquah</strong>; School of Medicine; University of Pittsburgh</td>
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<td>15:40 – 17:30</td>
<td>Welcome reception and poster walk and refreshments</td>
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Programme

Day 2

8 October 2015
08:00 – 09:00 Meet the Expert

Establishing North-South Collaboration
Emeritus Professor Kwaku Ohene-Frempong; Philadelphia and
Associate Professor Solomon Ofori-Acquah; University of Pittsburgh

Research Opportunities for Adult patients with a haemoglobinopathy
Professor Kathryn Hassell

Assessing and managing mental health in haemoglobinopathies
Dr Marsha Treadwell

09:00 – 11:00 Thalassaemia Plenary Session – Chair Dr Banu Kaya

Iron chelation in paediatric patients with haemoglobinopathies
Dr Banu Kaya; Department of Paediatric Haematology and Oncology, Barts Health NHS Trust, Royal London Hospital, London

Endocrine and bone complications in β-thalassemia: current understanding and treatment
Associate Professor Antonis Kattamis; First Department of Pediatrics; University of Athens, Athens, Greece

Guidelines for diagnosis and management of Beta – Thalassemia intermedia
Professor Ali Taher; Department of Internal Medicine, American University of Beirut Medical Centre, Beirut, Lebanon (Electronic Address)

Multiparametric Cardiac Magnetic Resonance Survey in Children with Thalassaemia Major; A Multicenter Study

11:00 – 11:15 Coffee Break

11:15 – 13:00 Parallel session C – Psychosocial theme – Chair Dr Marsha Treadwell

Body Image and Depressive symptoms in Jamaican Adolescents with Sickle Cell Disease
Komal Bhatt-Poulose; The University of the West Indies

Quality of life in children with sickle cell disease
Dr Jerlym Porter, PhD St. Jude Children’s Research Hospital

Quality of life and quality of care in adults with sickle cell disease
Dr Marsha Treadwell, PhD UCSF Benioff Children’s Hospital Oakland

Pain and quality of life in hospital for adults with sickle cell disease
Dr Kofi Anie PhD; Haematology and Sickle Cell Centre, London North West Healthcare NHS Trust, Central Middlesex Hospital, Acton Lane, London
11:15 – 13:00 Parallel session D – Complications in sickle cell disease in the adult patient – Chair: Dr Biree Andemariam, Department of Hematology, University of Connecticut SOM

A Study of the Geographic Distribution and associated Risk Factors of Leg Ulcers within an International Cohort of Sickle Cell Disease Patients: The CASIRE Group Analysis
Andrew Campbell; Director, Pediatric Comprehensive Hemoglobinopathies Program, Assistant Professor, University of Michigan

Stroke in adults with sickle cell disease: management options and challenges
Dr Moji Awogbade;
Department of Haematology, King's College London –

Aurora: Venous thromboembolism
Professor Kathryn Hassell; Professor of Medicine, Division of Hematology, Department of Medicine, University of Colorado Anschutz Medical Campus,

Pulmonary Hypertension in Sickle cell disease
Associate Professor Elizabeth Klings; The Pulmonary Center, Boston University School of Medicine, Boston, MA.

13:00 – 14:00 Lunch and Meet the Expert

Hydroxyurea therapy in Sickle Cell Disease
Professor Winfred Wang; St. Jude's Children's hospital, Memphis

The management of Thalassaemia including Thalassaemia intermedia
Professor Ali Taher

The Role Prevention in Thalassaemia
Associate Professor Antonis Kattamis; Athens

14:00 – 16:00 Parallel session E – Organ Disorders in Sickle Cell Disease – Chair Professor Sophie Lanzkron

Renal complications of Sickle Cell Disease
Dr Claire Sharpe; Department of Nephrology, King's College London

Impact of a dedicated infusion clinic for acute management of adults with sickle cell pain crisis
Professor Sophie Lanzkron; Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland

Avascular Necrosis in Sickle Cell Disease
Mr Marcus Bankes; Department of Orthopaedics, Guy's and St Thomas’ NHS Trust, London

Pregnancy in Haemoglobinopathies
Dr Eugene Oteng-Ntim; Department of Obstetrics, Guy’s and St Thomas’ NHS Trust
<table>
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<tr>
<th>Time</th>
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| 14:00 –16:00 | Parallel session F – Educational Session on Thalassaemia – Chair Subarna Chakravorty, Consultant Haemotologist Kings College | Managing the Cardiac Complications in Thalassaemia major  
**Dr Malcolm Walker**; Department of Cardiology, University College Hospital, London  
Evaluation of Endocrine functions in Hb E Thalassaemia patients with special reference to assessment of growth and puberty  
**Dipanjan Haldar**; Consultant Haematologist & Haematoncologist Wockhardt Hospitals Ltd.  
Cardiac MRI in Thalassaemia  
**Dr Alessia Pepe**; aCMR Unit, Fondazione ‘G. Monasterio’ CNR-Regione Toscana, Pisa  
bEmatologia-Emoglobinopatie, Civico ARNAS Hospital, Palermo  
Transfusion therapy for Thalassaemia – The ultimate goal  
**Dr Sara Trompeter**; Department of Haematology, University College Hospital, London |
| 16:00 – 16:30 | Tea Break | |
| 16:30 – 18:15 | Cure for Sickle Cell and Thalassaemia – Chair Professor Alexis Thompson | The relationship between genotype, alloantibodies and splenectomy on transfusion requirements in Beta Thalassaemia major  
**Jonah Fox**; Emory University School of Medicine  
Overview of Transplantation in Hemoglobinopathies  
**Professor Alexis Thompson**; Lurie Children’s Hospital Chicago, IL-  
Novel approaches to transplantation in sickle cell and thalassemia- newer data on unrelated donor and haploidentical transplants  
**Dr Josu De La Fuente**; Department of Haematology, Imperial College London and Imperial Healthcare NHS Trust, London  
Gene therapy in sickle cell disease and Thalassaemia – preclinical and clinical studies to date  
**Professor Marina Cavazzana**; Institut National de la Santé et de la Recherche Médicale, Unité 768, Paris, France |
Programme

Day 3

9 October 2015
### 9th Annual Sickle Cell and Thalassaemia Advanced Conference
7 – 9 October 2015

<table>
<thead>
<tr>
<th>Time</th>
<th>Session/Topic</th>
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<tbody>
<tr>
<td>08:00 – 09:00</td>
<td>Meet the Expert: A – Clinical Management</td>
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<td>Management of Acute Chest syndrome in sickle cell disease</td>
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<td>Dr Jo Howard; Department of Haematology, Guy's and St Thomas’ NHS Foundation Trust</td>
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<td>08:00 – 09:00</td>
<td>Meet the Expert: B – Nursing Management</td>
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<td>Development of a New Adult Sickle Cell Disease Center within an Academic Cancer Center: Impact on Hospital Utilization Patterns and Care Quality</td>
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<td>Biree Andemariam; Department of Hematology, University of Connecticut SOM</td>
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<td>Transition from Paediatric to Adult care</td>
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<td>Mr Luhanga Musumadi; Guy's and St Thomas’ NHS Foundation Trust</td>
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<td>Extended nursing role in patient care for haemoglobinopathies</td>
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<td>Mr Neil Westerdale; Guy's and St Thomas’ NHS Foundation Trust</td>
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<td>09:00 – 11:00</td>
<td>Parallel session G – Global Burden of SCD – Chair Dr Fred Piel</td>
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<td>Effects of Underweight Status on the Clinical Phenotype of an International Cohort of SCD Patients</td>
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<td>Biree Andemariam; Department of Hematology, University of Connecticut SOM</td>
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<td>Global burden of Sickle Cell Anaemia</td>
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<td>Dr Fred Piel, Oxford University, Oxford</td>
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<td>Lessons from 22 years in improving health of children and pregnant women with SCD in a Sub-Saharan Africa setting</td>
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<td>Professor Cherif Rahimy; Faculty of Health Sciences Cotonou, Benin Republic</td>
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<td>Addressing the challenge of Sickle Cell Disease</td>
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<td>Emeritus Professor Kwaku Ohene-Frempong; Children’s Hospital</td>
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<td>Philadelphia</td>
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<td>09:00 – 11:00</td>
<td>Parallel session H - CNS complications in SCD – Chair Dr Winifred Wang</td>
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<td>Exploring Health-Related Quality of Life and health behaviours in Children with Sickle Cell Disease</td>
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<td>Christina Constantinou; Doctoral Candidate, School of Science and Technology, Middlesex University</td>
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<td>Prevention and Management of Stroke in Sickle Cell Disease in Nigeria;</td>
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<td>Progress of the SPIN Trial</td>
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<td>Dr Najibah Galadanci; Department of Haematology and Blood Transfusion, Bayero University/Aminu Kano Teaching Hospital, Kano, Nigeria</td>
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<td>Neurocognition in Sickle Cell Disease</td>
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<td>Professor Fenella Kirkham; From the Development of Clinical</td>
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<td>Neurosciences Section, UCL Institute of Child Health, London</td>
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The Significance of Silent Cerebral Infarcts in Children with Sickle Cell Anaemia

Professor Winfred Wang; Department of Hematology, St. Jude Children’s Research Hospital, Memphis, TN, USA

11:00 – 11:30 Coffee

11:30 – 13:30 Parallel session K – Developing Clinical and Research Capacity for Haemoglobinopathies – Sub-Saharan Africa – Chair Dr Rosemary Ekong

Burden of Adult Sickle Cell Disease: Management and challenges
Dr Eugenia Vicky Asare; Ghana Institute of Clinical Genetics, Korle-Bu Teaching Hospital, Accra, Ghana

Perspectives in Genetics and Secondary Prevention in Sickle Cell Disease
Professor Ambroise Wonkam; Division of Human Genetics, Faculty of Health Sciences, University of Cape Town, Cape Town, Republic of South Africa

Sickle Cell Anaemia in Central Africa: Environment, Genetics and Clinical features
Professor Leon Tshilolo; Monkole/Centre de Formation et d’Appui Sanitaire (CEFA), Kinshasa, DR Congo

Gene-Disease Databases: Opportunities for research and development in sub-Saharan Africa
Dr Rosemary Ekong; University College London

11:30 –13:30 Parallel session L – Developing Clinical and Research Capacity for Haemoglobinopathies– Europe – Chair Dr Raffaella Colombatti

Evaluation of admissions to the Emergency Department of children with Sickle Cell Disease from 2006 to 2015 in Padova
Chiara Marra; Paediatric Emergency Unit Azienda Ospedaliera – University of Padova, Italy

Neglect of sickle cell disease in Germany: The example of newborn screening
Dr Stephan Lobitz; Charité – Universitätsmedizin Berlin, Klinik für Pädiatrie mit Schwerpunkt Onkologie/Hämatologie/KMT, Germany

Challenges for the management of sickle cell disease in France
Professor Mariane De Montalembert, Hôpital universitaire Necker-Enfants malades, France

The care of sickle cell patients in Italy: psychosocial issues and Hydroxyurea treatment availability
Dr Raffaella Colombatti; Azienda Ospedaliera-Università di Padova, Italy

13:30 – 14:30 Lunch
14:30 – 16:30  **Drug therapies in Sickle Cell and Thalassaemia – Chair: Dr Maria Pelidis; Department of Haematology, St Georges Hospital, London**

Impact of Hydroxyurea therapy on SCD in children: Brazilian experience  
**Professor Clarisse Lobo;** Clinical Hematology Division, Instituto de Hematologia Arthur de Siqueira Cavalcanti – HEMORIO, Rio de Janeiro, Brazil

New Drug Therapies in Thalassaemia  
**Professor John Porter;** Department of Hematology, UCL Cancer Institute, University College London, London, United Kingdom

New Drug therapies in Sickle Cell Disease  
**Professor Miguel Abboud;** Department of Pediatrics and Adolescent Medicine, American University of Beirut, Beirut, Lebanon –

Preview of 2016 Conference  
**Dr Rachel Kesse-Adu;** Evelina, Guy's and St Thomas’ NHS Trust, London

16:30 – 16:35  **Close**
Faculty
Conference director and Steering committee
Dr Baba Inusa | Course Director
Lead Consultant Sickle Cell and Thalassaemia Service,
Evelina London Children’s Hospital
Guy’s and St Thomas’ NHS Foundation Trust
Associate Professor, King’s College London UK

Dr Inusa graduated from ABU Zaria, Nigeria in 1984 after completing his postgraduate training in both Nigeria and the UK. He leads the sickle cell and thalassaemia service, Evelina Children’s Hospital, Guy’s and St Thomas’ Hospital (GSTT). He is the co-chair GSTT-Arthur Davidson Children’s Hospital, Zambia, national secretary for the UK Forum on Haemoglobin Disorders, founder and vice-chair of Sickle Cell Cohort Research (www.score-international.org) with the base in Abuja.

He serves on the American Society of Hematology (ASH) International Members Committee which is responsible for ASH visitors training programme (VTP), the committee are also developing strategy for ASH response to sickle cell burden. He has a passion for raising the standard of care for SCD in Nigeria and was awarded a European Community-United Nations Development Programme (EC-UNDP) for pilot SCD screening in Abuja. Dr Inusa’s main research is sickle cell disease and he has been appointed a Reader by King’s College London.

Dr Moji Awogbade | Steering Committee
Consultant Haematologist, King’s College Hospital

Dr Awogbade trained at the College of Medicine, University of Lagos. She undertook postgraduate training in the United Kingdom and completed specialist training in haematology in 2001.

Dr Moji Awogbade was appointed as a Consultant Haematologist at King’s College Hospital in 2003 and her specialist interest is in sickle cell disease. Her interests include the evolving understanding of the pathophysiology of sickle cell disease and the translation of this into effective treatment. Dr Awogbade was a contributing author to the Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK. She is involved in postgraduate training of doctors specialising in haematology.

Dr Banu Kaya | Steering Committee
Barts Health NHS Trust, Royal London Hospital, London

Dr Banu Kaya graduated from the United Medical and Dental School of Guy’s and St Thomas’ Hospital in 1998 and following completion of her specialty training joined Barts Health NHS as a consultant haematologist based within the departments of paediatric haematology and clinical haematology in 2006. In 2014 she became honorary Clinical Senior Lecturer, Barts and The London School of Medicine and Dentistry, Queen Mary University of London. She is a member of the Royal College of Physicians and Fellow of the Royal College of Pathologists. She has an interest in red cell disorders and paediatric haematology in addition to medical education, and she was previously the North East London Haematology Training Programme Director (2008-2014) and Chair of the Training Programme Management Committee, North East Central London, 2014. She is currently Co-Chair of the Paediatric Haemoglobinopathy Peer Review Programme and steering group, 2014-2016.
Faculty
Conference speakers and chairs
Dr Kofi A Anie | Consultant Psychologist
London North West Healthcare NHS Trust
Dr Anie trained at the University of Surrey and the University of London.

Dr Kofi Anie is responsible for the psychological services of children and adults with sickle cell disease and thalassaemia attending London North West Healthcare NHS Trust. This service includes an innovative Self-Help Cognitive Behavioural Therapy (CBT) programme, and Neuropsychology. Other appointments held are Honorary Clinical Senior Lecturer at Imperial College London.

He has a special interest in behavioural medicine and pain management, and began his professional career at King's College Hospital, London where he pioneered psychological interventions for children with sickle cell disease. He was later a Research Fellow at St George's Hospital Medical School in London where most of his work focused on chronic illness and pain, including sickle cell disease. He was appointed to his current position in 1998. Dr Anie is a Fellow of the Royal Society of Medicine and Associate Fellow of the British Psychological Society; his other professional affiliations include the British Association of Behavioural and Cognitive Psychotherapies, and American Psychological Association. He was involved in development of clinical guidelines and standards for sickle cell disease and thalassaemia, including NICE Guideline Development Group – Sickle Cell Acute Pain Episode and Expert Working Party for National Haemoglobinopathies Project. He is currently a Haemoglobinopathies Editor for the Cochrane Library, Scientific Advisor to Sickle Cell Society, and Advisor to Roald Dahl Marvellous Children's Charity.

Dr Anie's professional aspiration is owed to a personal family experience of sickle cell disease. His contribution to this area of work is acknowledged internationally. Research interests include sickle cell pain, quality of life, adherence to treatment, and eHealth and mHealth in patient self-management.

Mr Marcus Bankes | Department of Orthopaedics
Guy’s and St Thomas’ NHS Trust, London

Marcus’s practice is exclusively confined to problems in and around the hip joint, with a special interest in surgical treatment of young adult hip disorders. Marcus is the orthopaedic surgeon in the multidisciplinary service for sickle cell anaemia at Guy's Hospital. This team allows sickle patients to have safe and effective hip replacement surgery, a procedure that, in the past, was much less predictable. He has pioneered the use of un-cemented ceramic on ceramic hip replacements in this patient group.

Recognised as an opinion leader in hip surgery, Marcus gives between 10 and 20 talks a year to local and national meetings on the subjects of ceramic on ceramic total hip replacement, hip resurfacing, hip arthroscopy, hip dysplasia, hip impingement and the orthopaedic complications of sickle cell disease. He is a regular contributor at the British Hip Society, London Hip Meeting, and the British Orthopaedic Association as well as being a reviewer for a number of orthopaedic journals. He is Chair of the Steering Group for the British Non-Arthroplasty Hip Registry, the only registry in the world for hip preservation surgery and hip arthroscopy.
Dr Valentine Brousse | Senior Consultant
Hôpital Universitaire Necker-Enfants Malades, France

Dr. Valentine Brousse is a paediatrician specialising in haemoglobinopathies. She is a senior consultant working for the Reference Centre for Sickle Cell Disease in Necker Hospital, Paris where over 500 SCD children are followed, from neonatal diagnosis through transition to adulthood. She is specifically responsible for the Day Care Unit. She coordinates a clinical research program on predictive factors of severity in sickle cell disease children. She is also a collaborator in the INSERM team S 1134 “Integrated Biology of Red Blood Cells”, focusing on adhesion proteins on SCD red blood cells.

Andrew Campbell, MD | Director, Pediatric Comprehensive Hemoglobinopathies Program
University of Michigan
Director, The CASiRe Consortium

Dr. Campbell is a graduate of Case Western Reserve School of Medicine and he completed his residency training at Harvard Affiliated Massachusetts General Hospital, Boston. This was followed by a Pediatric Hematology/Oncology Fellowship at Northwestern University. Currently he is Assistant Professor of Pediatrics at the University of Michigan. He directs the Comprehensive Pediatric Hemoglobinopathies Program which includes the Pediatric Sickle Cell and Thalassemia clinic at the University of Michigan. He has served on multiple NIH Scientific Boards including the National SIT Trial and the Baby Hydroxyurea Study. He is on the National Advisory Board for Blood and Stem Cell Transplantation, appointed by the Dept. of Human and Health Services (HHS).

He is also Clinical Adjunct Professor in the Department of African Studies and a Faculty Associate for Global Reach Program at the University of Michigan. He is Co-Investigator the NIH-Fogarty Funded Minority International Health Research Training Program (MHIRT) where his research has focused on investigating the sickle cell phenotype in Ghanaian sickle cell patients. For the past few years he has focused his research in understanding the varied phenotypic expression of SCD in different populations through multinational CASiRe (Consortium for the Advancement of Sickle Cell Disease Research) International Consortium which he directs including Europe - Italy (University of Padova, University of Naples), and UK (Guy's and St Thomas'), North America – USA (University of Michigan, University of Toledo-Promedica Toledo Children's Hospital, University of Illinois Chicago, University of Connecticut, Albert Einstein-Montefiore, Case Medical Center-Rainbow Children's Hospital, Vanderbilt University, and Africa- Ghana (Korle Bu Teaching Hospital). The focus of the CASiRe sickle cell research is the “CASiRe Renal Cohort Study” which describes the risk factors associated with proteinuria in different SCD populations within different ethnic groups, including people of African, Caribbean, Arab, American, and European descent. They are also studying the role of the environment on the phenotype of Sickle cell disease.
Professor Marina Cavazzana | Institut National de la Santé et de la Recherche Médicale, Unité 768, Paris, France

Marina Cavazzana is a paediatrician, Professor of Haematology since 2000, and Director of the Department of Biotherapy at Hospital Necker, University Paris Descartes. She is the Director of the Inserm / Assistance Publique - Hôpitaux de Paris GHU Ouest Biotherapy Clinical Investigation Center and leads the Human Lymphohematopoiesis research Laboratory in Imagine Institut. She studied medicine in Padua, Italy and received the degree of Doctor of Medicine in 1983, her certification in Paediatrics in 1987 and a PhD in Life Sciences in 1993 (University Paris VII).

Her main research interests are development of the immune system, genetic diseases of the haematopoietic system and cell and gene therapy. She has initiated several clinical trials based on the use of ex vivo gene modified cells to treat patients with inherited disorders, the preliminary clinical results of which are encouraging. This work was rewarded by the American Society of Hematology (Award on Clinical Research in Gene Therapy in 1999), and by the French Academy of Sciences (Special Medical Award in 2000 and Jean-Pierre Lecocq Award on Gene Therapy in 2004). She was awarded the title of Officier de l’Ordre National de la Légion d’honneur in 2011, and given the Irène Joliot Curie 2012 award “Scientific Women of the Year” (Science Academy and French Ministry of Education and Research).

Dr Raffaella Colombatti | Pediatric Haematologist
Azienda Ospedaliera-Università di Padova, Italy

Dr Colombatti is Pediatric Hematologist at the Clinic of Pediatric Hematology Oncology of the Azienda Ospedaliera-Università di Padova. She trained at the University of Padova where she performed her pediatric residency, her fellowship in Pediatric Hematology Oncology and her PhD in Pediatric Hematology Oncology. Her main field of interest is sickle cell disease and she contributed to organise the Sickle Cell Clinic of Padova, which is Regional Reference Center for Sickle Cell Disease. She is a member of the Italian Association of Pediatric Hematology Oncology (AIEOP) Red Cell Disease working group and of the Sickle Cell Disease group. She is in charge of the Anemia Program at her institution. Dr. Colombatti is also interested in child global health and runs several programs in West Africa.

Christina Constantinou | Research Assistant
Middlesex University

Christina initially developed her knowledge of paediatric chronic conditions and her research skills through her educational development including her Master’s Degree in Health Psychology with Middlesex University. Since completing her studies Christina has attained clinical and research experience whilst working in the NHS and universities as a research assistant. Examples of research projects Christina has led include implementing questionnaires and semi-structured interviews to ascertain the general Quality of Life (QoL) of sixty-eight children and adolescents with chronic kidney disease, and also using focus groups to explore the QoL of twenty-six young people with cancer.

Christina is a fulltime MPhil/PhD candidate with Middlesex University. Her doctoral studies build on her published master’s research by focusing on Health-Related Quality of Life in paediatric sickle cell disease (SCD). She has adopted a mixed-methodological approach to ascertain a complete picture of the experiences of children and adolescents with SCD and their families, and how clinical manifestations and psychosocial factors associated with SCD may influence and be influenced by engaging in daily health behaviours as well as risky behaviours.

Christina is also currently employed by Middlesex University as a Research Assistant and Administrative Assistant on an ESRC funded project and also leads undergraduate seminars.
Dr Yvonne Danie PhD, CSci-FIBMS, MSc I Specialist Lead Scientist
Haematological Sciences and Special Haematology Lead at Viapath, Guy's & St Thomas' Hospital London.

Dr Daniel has worked in laboratories in both New Zealand and the UK specialising in haemoglobinopathy diagnosis since 1995. Her experience encompasses protein, including mass spectrometry and molecular based diagnostic techniques. Dr Daniel's was seconded as a scientific advisor to the NHS Sickle Cell & Thalassaemia Screening Programme since 2010 and involved as a scientific advisor for projects implementing HPLC based haemoglobinopathy screening in Abuja and Katsina, Nigeria and Dar Es Salam, Tanzania.

Dr Rosemary Ekong | Human molecular geneticist
University College London

Dr Rosemary Ekong, PhD, is a human molecular geneticist whose work has covered gene mapping and genomic variation. Her current focus is on the role of genetic variants in normal health and disease. Her work on defined populations has contributed to resources for further medical research. Rosemary's interest in Tuberous Sclerosis (TSC) and difficulties in ascertaining the clinical significance of variants identified in genetic testing led to her curating the publicly available TSC variation databases, a role in which she also advises TSC clinicians and clinical geneticists. She has served as a member of the Human Variome Project (HVP) Data Collection Working Group and the Genetics Working Group (TSC Natural History Database). She currently serves as a member of the HVP Gene/Disease Specific Database Advisory Council and chairs the HVP Ethics Working Group. Rosemary has a continued interest in ethical data sharing to aid further research and improve patient care.

Dr Najibah Aliyu Galadanci, MBBS MPH FMCPath I
Department of Haematology and Blood Transfusion, Bayero University/Aminu Kano Teaching Hospital, Kano, Nigeria.

Najibah has been working in the department of hematology in Bayero University and Aminu Kano Teaching Hospital, northern Nigeria for over 9 years now, initially as a resident doctor and later a lecturer and consultant hematologist. Practicing as a clinician and a laboratory physician in Kano, northern Nigeria, Najibah has had a great opportunity to see a lot of cases of hematological disease, including sickle cell disease. As a hematologist with a special interest in sickle cell disease, Najibah's research experience has been focused mainly on this area. Najibah received the prestigious David Satcher Award for a Masters in Public Health at Vanderbilt University (2013) and has just concluded their MPH program in May 2015.

More recently, Najibah is the site investigator of the first NIH funded Primary Prevention of Stroke in Children with Sickle Cell Disease in Nigeria trial (1R21NS080639-01). They also served as the lead site investigator in a multicenter study on Asthma in Children with Sickle Cell Disease in Kano, Nigeria that was funded by Vanderbilt endowed chair funds, and is am currently a co-investigator in the feasibility study of establishing a prospective cohort of pregnant women with sickle cell disease, a multicenter study aim at establishing the largest cohort of pregnant women with SCD in Nigeria and Ghana. In June 2014 Najibah received an NIH funded Fogarty Fellowship Award to conduct a research on secondary stroke prevention for children with sickle cell disease in Nigeria.
Professor Kalpna Gupta | Professor of Medicine
University of Minnesota Medical School co-Leader of the Molecular and Cellular Engineering Program at the Institute for Engineering in Medicine

Kalpna Gupta, PhD is a Professor of Medicine in the Division of Hematology, Oncology and Transplantation; and co-Leader of the Tumor Microenvironment Program in the Masonic Cancer Research Centre; and Molecular and Cellular Engineering Program at the Institute for Engineering in Medicine, at the University of Minnesota, Minneapolis, Minnesota, USA. She obtained her PhD from the All India Institute of Medical Sciences (AIIMS), New Delhi, India. She was an associate professor of biochemistry at AIIMS until she moved to the United States.

Dr Kalpna Gupta is a leading investigator in research on pain and vascular biology in sickle cell disease (SCD). Her seminal observations on morphine signaling in endothelium laid down the foundation to understand the role of opioids in cancer progression. Simultaneously, she initiated investigation on understanding the neurobiology of pain in SCD. Her basic findings are under clinical studies/trials currently.

She has a strong track record of receiving highly competitive NIH funding for pain and opioid biology research. She is a recipient of the Excellence in hemoglobinopathies Research Award from NHLBI, NIH, to study cannabinoid-based therapy and approaches to quantify pain in sickle cell disease.

Her research interests are global. She received the Science without Borders award from the Government of Brazil to advance their endeavors in sickle cell disease research.

Dr Gupta is a standing member of the hypertension and microcirculation study section and serves as an ad-hoc member for several study sections at NIH. She is a member of the Advisory Council for Sickle Cell Disease at NIH. She is a reviewer for several high impact peer reviewed journals including, Nature Publishing group, Lancet, Blood, Cancer Res, J Biol Chem, etc. She has authored over 60 peer-reviewed publications, several reviews and book chapters.

Dr Gupta is highly involved in the graduate teaching programs for fellows in medicine and graduate students in the Cancer Centre. She has mentored several fellows and post-docs. She is extremely active in promoting diversity in medicine. She serves as a member of the Admissions Executive Committee for MD admissions, University of Minnesota.

Mrs Yvonne Harrington | BMT co-ordinator
Imperial College Healthcare NHS trust

Yvonne Harrington qualified in 2004 with a Bachelor of Science in child health nursing from Thames Valley University, London. She began her career in paediatric haematology as a staff nurse in the bone marrow transplant unit at St Mary's Hospital, Imperial College Healthcare NHS trust. In 2005 Yvonne was employed at Great Ormond Street Hospital to focus on malignant haematology and bone marrow transplantation. She returned to Imperial College Healthcare in 2006 where she commenced her current role of BMT co-ordinator, responsible for the admission of children and young people for bone marrow transplant for haemoglobinopathies and bone marrow failure syndromes. Yvonne is a member of the EBMT nurses group.
Professor Kathryn Hassell | Professor of Medicine
University of Colorado

Dr. Hassell is a Professor of Medicine in the Hematology Division at the University of Colorado, Denver and directs the Colorado Sickle Cell Treatment and Research Center. She also supervises the Hemoglobinopathies Newborn Screening Follow-Up Program for the states of Colorado and Wyoming. She has an academic clinical practice at the University of Colorado, where 150 adults living with sickle cell disease are managed, and also offers a large thrombosis consultative service, plus she supervises a pharmacy-directed warfarin monitoring clinic with over 600 patients. For more than 20 years, Dr. Hassell has been actively involved in the design, conduct and monitoring of clinical research studies in hemoglobinopathies, with an emphasis on adult sickle cell disease, and in venous thrombosis, with an emphasis on new anticoagulants. She has served on and chaired international steering committees for multi-center trials as well as data/safety monitoring boards. Dr. Hassell has participated in multiple national projects sponsored by the NIH, HRSA, and CDC related to clinical research, health services, and disease management guideline development.

Jo Howard | Consultant Haematologist
Guy's and St Thomas' NHS Foundation Trust, London, UK
Honorary Reader in Clinical Haematology
King's College London, UK

Jo Howard is a Consultant Haematologist at Guy's and St Thomas' Hospital in London, Clinical Lead for Haematology and head of the Adult Sickle Cell Service. She graduated from the University of Cambridge in 1992 and subsequently trained in haematology in London, starting work as a consultant in 2002.

Dr Howard’s main research interest has been in developing and running clinical trials for the treatment of patients with sickle cell disease and she has been involved in international multi-centre trials (including TAPS) and in phase 1 and 2 trials in new agents. She is involved in quality improvement of sickle services in the UK and is Co-Chair of the National Peer review of Haemoglobinopathy Services and has been involved in writing national clinical guidelines.

Dr Vishal Jayakar MD, MRCP, FRCPath | Consultant Haematologist
Kingston NHS Foundation Trust
Honorary senior lecturer- Imperial College, London

Dr V Jayakar runs the popular FRCPath Revision Courses at Kingston for exam –going haematology trainees, which are widely subscribed from the UK, Ireland, UAE, India, Singapore and Hong-Kong. He is the Co-Organiser of the Imperial Morphology Courses along with Prof Barbara Bain. Apart from education, his main interests are morphology and myeloproliferative neoplasms.
Antonis Kattamis | First Department of Pediatrics
University of Athens, “Aghia Sofia” Children’s Hospital, Athens, Greece

Antonis Kattamis is Associate Professor of Paediatric Hematology–Oncology at the University of Athens. He received his MD degree (cum laude) in 1988 from University of Athens. He completed his training in paediatrics at the University of Texas Health Science Center in San Antonio, USA and in paediatric hematology–oncology at the Children’s Hospital of Philadelphia, University of Pennsylvania School of Medicine, USA.

He is head of the division for hematology-oncology within the First Department of Paediatrics, where in the thalassemia unit, more than 400 regularly-transfused patients with congenital anemias are followed.

He has published more than 90 articles, mainly in the field of hemoglobinopathies and of iron metabolism.

Fenella Kirkham | Development of Clinical Neurosciences Section, UCL Institute of Child Health, London

Dr Kirkham was an undergraduate at Girton College, Cambridge and followed up her second MB with a BA in history and philosophy of science (1975). After clinical training at Kings’ College Hospital (MB 1978 BChir 1979), where she particularly enjoyed child health and neurology, she went straight into paediatrics. From 1982 she undertook a research project on Coma in childhood at Guy’s hospital, supervised by Dr Brian Neville and funded by the British Heart Foundation, which formed the basis of her MD. She trained as a paediatric neurologist and held an honorary clinical consultant post at Great Ormond Street Hospital until 1999, when she moved to University Hospital Southampton Trust as a consultant paediatric neurologist. She has been Dr at UCL Institute of Child Health since 2006 and at the University of Southampton since 2007.

Dr Kirkham’s research focuses on the prediction and prevention of complications, particularly neurocognitive, in sickle cell disease. In building up a cohort with up to 30 years follow-up so far, she collaborates with haematologists and paediatricians in the UK. Dr Kirkham was the principal investigator on a pilot randomised controlled trial of overnight auto-adjusting CPAP, funded by the Stroke Association (UK), which suggested that some of the morbidity in this condition (pain and poor attention) is preventable. She was also the chief investigator for the London site on two international collaborative studies: a cohort study ‘Asthma and nocturnal hypoxemia in sickle cell anemia’ (National Heart Lung and Blood Institute, USA) and a randomised trial of blood transfusion-the ‘Silent Infarct Transfusion Trial’ (National Institute for Neurological Diseases and Stroke, USA). Dr Kirkham now has funding from NIHR Research for Patient Benefit for a Phase 2 trial of overnight respiratory support in adults and children at Guy’s and St Thomas’ and King’s College Hospital NHS Foundation Trusts.
Dr. Elizabeth Klings is an associate professor of medicine at Boston University School of Medicine, the director of the Center for Excellence in Sickle Cell Disease and an attending physician in the Section of Pulmonary, Critical Care and Allergy at Boston Medical Center. She came to Boston University after receiving Bachelors of Arts and Doctor of Medicine degrees at New York University in New York. She completed her residency in internal medicine at Boston City Hospital and fellowship training in pulmonary and critical care at Boston University School of Medicine. She joined the faculty at Boston University in July 2000 and currently directs the Inpatient and Education Programs of the Pulmonary Hypertension Center and is medical director of the Pulmonary Rehabilitation Program at Boston Medical Center. Since fellowship, her clinical and research interests have focused on pulmonary vascular complications of sickle cell disease. In March 2015, she became the director of the Center for Excellence in Sickle Cell Disease which cares for 200 adults and 250 children and adolescents with sickle cell disease. She has published over 35 papers and book chapters on this subject. Recently, she led a committee of adult and pediatric pulmonologists, cardiologists and hematologists to develop the first-ever Clinical Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension in Sickle Cell Disease, published in the American Journal of Respiratory and Critical Care Medicine and funded by the American Thoracic Society.

Professor Sophie Lanzkron is an Associate Professor of Medicine and Oncology in the Division of Hematology at the Johns Hopkins University School of Medicine and is the Director of the Sickle Cell Center for Adults at Johns Hopkins which delivers state-of-the art, multidisciplinary care to over 500 patients. She is internationally recognised for her pioneering research on the optimal care and management of patients with sickle cell disease. She has served on the National Institute of Health, Expert Panel in the Management of Sickle Cell Disease and is an NIH and PCORI funded researcher. Her research focus is on improving the quality of care provided to this historically underserved population and she is considered an expert in health services research in sickle cell disease.

Dr. med. Stephan Lobitz, MSc is a consultant in paediatric haematology and oncology at Charité University Hospital in Berlin. He studied medicine in Düsseldorf and Berlin and is holds a postgraduate MSc degree in haemoglobinopathies from the University College London.

Dr Lobitz is the speaker for the German Paediatric Sickle Cell Disease Programme and the corresponding author of the German treatment guideline. His special interest is in newborn screening for SCD which has not been implemented in Germany until now.
Dr. Clarisse Lobo
Instituto de Hematologia Arthur de Siqueira Cavalcanti

Clarisse gained her Bachelor Degree in medicine at the State University of Rio de Janeiro, Brazil, Specialization in haematology and haemotherapy at Federal University of Rio de Janeiro, her Master Degree in health management and hospital administration and PhD, ongoing, at the Federal Fluminense University.

She began her medical career as a haematologist at Hemorio - State Hematological Hospital and Rio de Janeiro State Regional Blood Center. She has occupied various positions of increasing medical and administrative responsibilities, such as Head Hematological Service, Hospital Technical Director and CEO of Hemorio.

She has published several papers in national and international journals. Her increasing profound technical knowledge and leadership skills have led to participation in several technical boards and research groups.

Professor Sebastian Lucas FRCP FRCPath
Guy’s & St Thomas’ Hospital

Sebastian Lucas was the professor of pathology at Guy’s & St Thomas’ Hospital from 1995-2012, and is now emeritus. He has been interested in the pathology of sickle cell disease since encountering it in Kenya in the early 1980s. He has a wide experience of the pathology of sickle cell patients who have come to autopsy in London, along with much referred case work from other pathologists. Over the last thirty years, the clinical pathology of severe and fatal sickle cell disease has changed along with improved management protocols, and his presentation reflects these different patterns.

Dr Maria Pelidis
St George’s university hospitals NHS foundation trust

Dr Maria Pelidis earned her MD from Harvard Medical School, United States. She went on to take a residency in paediatrics at the Children’s Hospital of Philadelphia, and a fellowship in paediatric haematology and oncology at Johns Hopkins University, Baltimore. She is a consultant in paediatric haematology and her clinical interests include haemoglobinopathies, iron overload, iron deficiency, bleeding disorders, bone marrow failure, leukaemia and lymphoma.

Dr Stephan Menzel, MD
Molecular Geneticist
King’s College London

Stephan is a geneticist studying sickle cell disease and the persistence of fetal haemoglobin at King's College London. His broader interests include genetic mapping of measurable (quantitative) traits in humans; disease and trait inheritance in families, and the population-genetic basis of ethnic trait differences. The sickle cell genetics group at King's has identified two major HbF/sickle cell disease modifier genes. Working with patients from all over the world, Stephan is fascinated by the fact that sickle cell disease, despite of the simple basic gene defect, can be a very diverse clinical condition, dependent on the patients’ genetic background.
Professor Mariane De Montalembert | Associate Professor of Paediatrics
Hôpital universitaire Necker-Enfants malades, France

Professor de Montalembert received her MD from the Paris Descartes Medical School in 1982 and her PhD in Ethics in 1994. She specialised in pediatrics, statistics (option clinical research), and transfusion. She is Associate Professor of Paediatrics and serves as the head of the Hemoglobin Diseases Unit at the Necker University Hospital, and the ROFSED healthcare network for SCD children in the Parisian area. Professor de Montalembert is a member of the French Society of Paediatrics, in which she chairs the Ethic Committee, of the French Society of Haematology, the European Network for Rare and Congenital Anaemias (ENERCA), the European Association (EHA), and the American Society of Hematology (ASH). She coordinates and participates in several clinical trials, especially on hydroxycarbamide use in SCD.

Luhanga Musumadi (BSc Hons, RGN, MPH) | Lead Nurse
Guy’s and St Thomas’ NHS Foundation Trust

Luhanga Musumadi (BSc Hons, RGN, MPH) is an ANP and Lead Nurse for the transition of adolescents with haemoglobinopathies at Guy’s and St Thomas’ NHS Foundation Trust, which includes the Evelina London Children’s Hospital. This post was the first of its kind in the country within haemoglobinopathies. He joined Guy’s and St Thomas’ in 2008 to set up the transition service, the service provides support for young people from the age of 13 to 24 years old. Prior to this he worked as a charge nurse at the Sickle cell & Thalassaemia Centre in Birmingham. Luhanga also lectures on the adolescent care module for graduate nurses at King’s College University London.

Solomon F. Ofori-Acquah, PhD | Associate Professor and Director
Center for Translational and International Hematology
Vascular Medicine Institute, University of Pittsburgh

Dr. Ofori-Acquah is an Associate Professor of Medicine at the University of Pittsburgh. His research is focused on the role and mechanism of extracellular heme in the pathobiology of acute and chronic pulmonary complications of sickle cell disease. He has developed a mouse model of acute chest syndrome (ACS) that recapitulates the clinical, biological and pathological features of the condition in humans. His model defined extracellular heme as a prototypical erythroid danger associated molecular pattern molecule that drives sterile inflammation in sickle cell disease in the absence of infection. He is using this model to tease out the mechanism of lung injury in ACS, and to test candidate drugs for their potential to prevent and treat this lung condition. His research on chronic effects of heme are focused on the role and mechanism of the Nrf2 pathway in end-organ damage in animal models of SCD, as well as in patients enrolled in large longitudinal cohorts in Africa.

Kwaku Ohene-Frempong, MD
Dr. Ohene-Frempong, originally from Ghana, received undergraduate and medical education at Yale University, USA. After a residency in pediatrics at New York Hospital-Cornell Medical Center, he completed a paediatric haematology fellowship at the Children’s Hospital of Philadelphia (CHOP), University of Pennsylvania.

With a long career in sickle cell disease Dr. Ohene-Frempong is currently Professor-Emeritus of Pediatrics at the University of Pennsylvania, Attending Hematologist and Director Emeritus of the Comprehensive Sickle Cell Center, CHOP, and President of the Sickie Cell Foundation of Ghana. He is also Programme Coordinator, National Newborn Screening Programme for Sickle Cell Disease in Ghana.
Dr Eugene Oteng-Ntim

Department of Obstetrics, Guy’s and St Thomas’ NHS Trust

Dr Eugene Oteng-Ntim graduated in medicine from Guy’s and St Thomas’ Medical School. He has worked mainly in London for 22 years specialising in obstetrics and gynaecology. In 2004 he became a consultant obstetrician and honorary senior lecturer at Guy’s and St Thomas’ NHS Foundation Trust. He has recently completed his tenure as head of obstetrics at Guy’s and St Thomas’ from 2010 to 2014. In 2003 he was awarded GlaxoSmithKline fellow by Royal Society of Medicine and in 2007 became president of the maternity and newborn section at RSM.

Dr Oteng-Ntim is a fellow of RCOG (Royal College of Obstetricians and Gynaecologists). He was admitted as a member of RCOG in 1997 and a fellow in 2009. He recently received a PhD in Epidemiology and Population Health from The London School of Hygiene and Tropical Medicine. He has published extensively, including in the British Medical Journal (BMJ) and Blood on Sickle Cell disease in Pregnancy and Obesity in Pregnancy. He was the lead author on the recent National Guideline on the Management of Sickle Cell Disease in Pregnancy.

Dr Mary Petrou

Dr Mary Petrou is an honorary senior lecturer at the Institute for Women’s Health, University College London (UCL), the Head of the Haemoglobinopathy Genetics Centre at University College London Hospitals NHS Foundation Trust, and a senior researcher for the Centre for Health Informatics and Multiprofessional Education (CHIME) University College London. Dr Petrou is also the Head of the Haemoglobinopathy Genetics Centre; providing a holistic prevention and risk assessment service for patients and their families including screening, genetic counselling and prenatal diagnosis (fetal sampling and molecular genetics) for the haemoglobinopathies.

Her current research involves developing non invasive methods for prenatal diagnosis. Dr Petrou has trained over 50 health professionals from around the world in prevention models including screening, genetic counselling and laboratory aspects of prenatal diagnosis; trainees have returned to their countries to set up prevention services. She is a member of the APoG1(Accessible Publishing of Genetic Information) team with Prof Modell and Dr Darlison, developing new web based information materials on haemoglobin disorders for patients and health professionals. She is an advisor to the United Kingdom Thalassaemia Society (UKTS), board member of the Genetic Alliance UK, and a member of the steering committee for the National Haemoglobinopathy Register (NHR) as well as a committee member of the UK Forum for Haemoglobin Disorders.

She has published in peer reviewed journals and chapters in books, and she was multi editor and author of two books for Thalassaemia International Federation prevention: Prevention of Thalassaemia and other Haemoglobin Disorders Vol 1 and 11.
Dr Frédéric B. Piel
University of Oxford, Oxford, UK

Fred Piel graduated in Geographical Sciences with 1st Honours at the Université Libre de Bruxelles (ULB) in 2000. He completed a PhD in the Biological Control and Spatial Ecology Lab (LUBIES, lubies.ulb.ac.be) at ULB in 2006, before joining the Malaria Atlas Project (MAP, www.map.ox.ac.uk) at the Department of Zoology, University of Oxford in 2007 to lead a new global initiative on inherited haemoglobin disorders in humans. In 2012, he moved to the Evolutionary Ecology of Infectious Disease (EEID, www.eeid.ox.ac.uk) within the same department before becoming Departmental Lecturer in Disease Genetics in 2013.

Fred’s research focuses on the epidemiology and health burden of inherited disorders of haemoglobin, sickle-cell disease in particular but also the thalassaemias, haemoglobin C, the Duffy blood group and G6PD deficiency. His work aims at using rigorous quantitative methods (including geostatistics and spatial models) to assemble contemporary evidence for informing public health policies to prevent and manage these disorders, and ultimately improving the quality of life of patients. In the last 9 years he has developed a large global network of international collaborators and has been published in prestigious medical journals, including The New England Journal of Medicine, The Lancet, The Lancet Global Health and PLOS Medicine. He is an expert of haemoglobinopathies for the Global Burden of Disease (GBD) Study and a member of the Editorial Board for the Transactions of the Royal Society of Tropical Medicine & Hygiene.

Prof. Antonio Piga
Division of Pediatrics & Thalassemia Centre
Dept. of Clinical and Biological Sciences, Torino University
San Luigi Gonzaga University Hospital

Antonio Piga is Professor of Pediatrics at the University of Torino, where he teaches pediatrics and evidence based medicine. After graduating in medicine he specialised in pediatrics and hematology. He served as president of the Medical Libraries of University of Torino and coordinator of the Health System Digital Library of Piemonte. He is chief in charge of the Division of Pediatrics and Thalassemia Centre of the S. Luigi University Hospital of Orbassano, where he leads the Transfusional and Chelation Programs, and the Prevention and Prenatal Diagnosis Program.

He developed the SQUID biosusceptometry and MRI Program that allows the non-invasive body iron assessment of more than 2000 patients per year. He also acts as scientific coordinator of the Webthal Project, a thalassemia network based on a computerized clinical record.

He is scientific advisor for several patient associations, including the Thalassemia International Federation. As PI or co-Investigator on several university and industry-funded grants, he collaborated to design and carry out phase I-III clinical trials on rare diseases, mainly thalassemia and sickle cell anaemia. He served as clinical advisor for the drug deferiprone during the approval process at the EMEA and FDA. He acts as peer reviewer for medical journals as Circulation, Blood, Cochrane, American Journal of Hematology, Haematologica, Journal of Pediatric Hematology Oncology, European Journal of Pediatrics. He is author or co-author of more than 150 publications in peer-reviewed journals. Research Fields include thalassemia and hemoglobinopathies, disorders of iron metabolism, non invasive methods for body iron assessment, medical librarianship, evidence-based medicine and drug development, in particular iron chelators, pathogen inactivation in blood products and modulators of bone marrow activity.
Jerlym Porter, PhD, MPH
Assistant member in the Department of Psychology
St Jude Children's Research Hospital

Jerlym Porter, PhD, MPH is an Assistant Member in the Department of Psychology at St. Jude Children's Research Hospital. She obtained a PhD in counseling psychology at Virginia Commonwealth University. She completed her predoctoral internship at Rush University Medical Center and postdoctoral training at the Center for Healthcare Studies at Northwestern University, Feinberg School of Medicine. During fellowship, she obtained an MPH within the Department of Preventive Medicine, Northwestern University. Dr. Porter's work focuses on improving quality of life for pediatric patients with SCD, with an emphasis on issues relevant to the transition from pediatric to adult care. Current projects include identification of transition predictors and outcomes, assessment of medication adherence, and characterization of nocturnal enuresis among youth with SCD.

Professor John Porter

Associate Professor Charles Quinn; medical director of the Erythrocyte Diagnostic Laboratory
Cincinnati Children's Hospital

Dr. Quinn’s clinical and research focus is sickle cell disease. His specific research interests include the morbidity, mortality, and long-term outcomes in SCD; the prediction of adverse outcomes; the pathophysiology, prevention and treatment of stroke; and the cardiomyopathy of SCD. Dr. Quinn is the medical director of the Pediatric SCD Program and the medical director of the Erythrocyte Diagnostic Laboratory at Cincinnati Children’s Hospital Medical Center (CCHMC). He is co-PI on the NIH-NHLBI Excellence in Hemoglobinopathies Research Award (EHRA) to CCHMC that supports ongoing studies of the cardiomyopathy of SCD.

Charles Quinn
Associate Professor
Medical director of the Erythrocyte Diagnostic Laboratory Cincinnati Children's Hospital

Dr. Quinn’s clinical and research focus is sickle cell disease. His specific research interests include the morbidity, mortality, and long-term outcomes in SCD; the prediction of adverse outcomes; the pathophysiology, prevention and treatment of stroke; and the cardiomyopathy of SCD. Dr. Quinn is the medical director of the Pediatric SCD Program and the medical director of the Erythrocyte Diagnostic Laboratory at Cincinnati Children’s Hospital Medical Center (CCHMC). He is co-PI on the NIH-NHLBI Excellence in Hemoglobinopathies Research Award (EHRA) to CCHMC that supports ongoing studies of the cardiomyopathy of SCD.
Dr Mohamed Cherif Rahimy  
Faculty of Health Sciences Cotonou, Benin Republic

Dr. Rahimy graduated from the Faculty of Health Sciences of Cotonou, Benin in 1982, following which he went to Paris for extensive postgraduate training in paediatrics at several teaching hospitals. He was conferred paediatrician in 1987 at U.E.R Necker – Enfants Malades of the University Rene Descartes Paris V.

He then practiced and furthered his training in paediatrics, immunology and haematology as senior registrar at the Teaching Clinic of Pediatric Immunology and Hematology in Hôpital Robert Debre of Faculté de Médecine Laribosière Saint Louis University Paris VII France under the late Professor Etienne Vilmer. He gained lot of experiences in clinical management of all aspects of paediatric haematology and immunology, genetics, bone marrow transplantation, paediatric HIV infection and malaria infection. He actively participated in many innovative treatment projects including the use of human cord blood as source of stem cells for bone marrow transplantation and the concept of PCR Conversion, which lead to the strategy of prevention of mother-to-child transmission of HIV.

In January 1993, after extensive training and despite several solicitations to pursue his career in France, he decided to return back to Benin where he was perfectly aware that the conducive environment and research facilities he was used to did not exist. Upon return, in addition to teaching paediatrics at the University of Benin and practicing at the National Teaching Hospital in Cotonou, he set up the first Neonatal Screening Program for Sickle Cell Disease (SCD) as well as a Comprehensive Clinical Care Program in Sub-Saharan Africa. The specifically tailored strategy he implemented has been deemed relevant to the unique conditions of African countries with outstanding scientific papers published in top-ranking journals in the field. He organised several regional training courses and international congresses in Cotonou on this inherited condition, which obviously is a neglected but important contributor to the burden of under-five deaths in Sub-Saharan Africa. His determination and skill of advocacy convinced his Health Authorities and Government to institutionalise a national program and to come forward to finance a separate building construction entirely devoted to children with SCD’s care and research.

On the occasion of the inauguration of this unique institution, he brought together SCD clinical and research experts (more than 80) from around the world to form a global network to advance patients’ care through global research.

His actions were also instrumental to the recognition of sickle cell anemia as a public health problem by the Heads of State of the Africa Union (Assembly/AU/dec. 81(V), 2005), the World Health Assembly (Resolution WHA 59.20 of May 27, 2006) and by United Nations General Assembly (Resolution A/RES/63/237 of December 22, 2008).

Finally, he was the head of the Writing Committee of Sickle cell disease prevention and control: A Strategy for the WHO African Region adopted by the general assembly of the Ministries of Health during the WHO-AFRO regional Committee (Resolution AFRO/RC60/8, August 30, 2010).

Professor David Rees | Paediatric haematologist
King’s College Hospital, London

David Rees is a paediatric haematologist at King’s College Hospital, London. He has research and clinical interests in paediatric sickle cell disease and other inherited red cell abnormalities. He has previously worked in London, Oxford and Sheffield and spent six years at the Weatherall Institute of Molecular Medicine in Oxford. He is involved in the care of more than 500 children with sickle cell disease.
Dr Noémi Roy | Academic Clinical Lecturer
Molecular Haematology Unit, Oxford University

Noémi Roy is an Academic Clinical Lecturer in Haematology at the University of Oxford. She studied acquired thalassaemia in MDS and the DNA methylation of the alpha globin locus in malignancy under Prof Higgs and attained her DPhil in 2012. Since then, her main research interest has been in rare inherited anaemias and she has set up a molecular diagnostic test for the investigation of congenital anaemias in Oxford, as well as an unexplained anaemia clinic. Clinically, she is part of the service which cares for patients with all red cell disorders, including sickle cell disease and thalassaemia.

Dr Claire Sharpe | Clinical Senior Lecturer
Department of Nephrology, King’s College London, Honorary Consultant in renal medicine

Claire Sharpe is a Clinical Senior Lecturer and Honorary Consultant in Renal Medicine at King’s College London/King’s College Hospital. She graduated in medicine from University College London and after specialising in renal medicine commenced research in renal fibrosis at King’s College London. She received a National Kidney Research Fund Clinical Training Fellowship in 1999 and was awarded her PhD in 2001. In 2002 she successfully obtained a Department of Health/NIHR 5-year Clinician Scientist Award and completed her specialist clinical training in 2004. In 2009 she was awarded a NHS/HEFCE Clinical Senior Lectureship and currently works as a clinical academic devoting 50% of her time to research and 50% to clinical activity. Her main research interest is in the study of the role of ras monomeric GTPase-dependent cell signaling pathways in renal fibrosis with a view to discovering new therapeutic targets. Her clinical research interests are in the clinical manifestations and pathophysiology of sickle cell nephropathy and in the epidemiology of cardiovascular disease in patients with chronic kidney disease.

Claire has been involved in the combined renal and sickle cell clinic at King’s College Hospital since it began in 2004. She has developed a strong interest in the underlying mechanisms and management of sickle cell nephropathy and is actively involved in studying both its epidemiology and the outcomes of early treatment. The clinic focuses on patient education, early intervention and on-going monitoring with the aim of slowing disease progression and minimising the number of patients who require renal replacement therapy in the long run.
**Professor Alexis Thompson | Hematology Section Head**  
Lurie Children's Hospital Chicago, USA

Dr. Alexis Thompson is currently the Hematology Section Head at Ann and Robert H. Lurie Children's Hospital of Chicago in Chicago, Illinois. She holds the A. Watson and Sarah Armour Endowed Chair for Blood Diseases and Cancer at Lurie Children's. She is also a professor of pediatrics at the Northwestern University Feinberg School of Medicine. Her clinical interests include hemoglobinopathies (thalassemia and sickle cell disease), bone marrow failure syndromes and stem cell transplantation in pediatric patients. Dr. Thompson is also the Associate Director for Equity and Minority Health at the Robert H. Lurie Cancer Center and Northwestern University Feinberg School of Medicine. Nationally she serves as a councilor on the Executive Committee of the American Society of Hematology as well as the DHHS Secretary's Advisory Committee on Heritable Disorders of Newborns and Children. She is an investigator on multi-center trials in her current position, as well as on her own institutional clinical studies in thalassemia, sickle cell disease and ITP.

Dr. Thompson received her MD from Tulane University School of Medicine. She also holds a Masters in Public Health from the University of California, Los Angeles in Health Services. Dr. Thompson completed her post-graduate training in pediatrics at Children's Hospital of Los Angeles, and then completed a fellowship in pediatric hematology/oncology at Children's Hospital of Philadelphia. After her fellowship, Dr. Thompson returned to her native California and joined the faculty at UCLA where, among other things, she was Director of the UCLA Sickle Cell Anemia Program; served on the UCLA Hospital Cancer Committee, the Blood and Blood Derivatives Committee; and was Associate Professor in the Department of Pediatrics at UCLA School of Medicine.

**Dr Marsha Treadwell | Clinical Psychologist and Researcher**  
UCSF Benioff Children's Hospital Oakland

Dr. Treadwell is a clinical psychologist and a clinical and health services researcher at UCSF Benioff Children’s Hospital Oakland in Oakland, CA, USA. Research interests include: cross cultural models of health beliefs and practices; patient reported outcomes (assessment and measurement development); transition from pediatric to adult care; adherence with medical regimens; and factors influencing pain experiences. Dr. Treadwell is co-principal investigator for the Pacific Sickle Cell Regional Collaborative that aims to improve sickle cell disease clinical services and policy, and enhance workforce development. Dr. Treadwell is co-investigator on Exploring Perspectives on Genomics and Sickle Cell Public Health Interventions, an H3Africa consortium project. Dr. Treadwell obtained her PhD in clinical psychology from the University of Washington in Seattle, WA USA and her training in clinical research from the Department of Epidemiology and Biostatistics at UCSF.

**Dr Sara Trompeter | Lead consultant of the Paediatric Red Cell Service**  
University College London Hospitals, UK

Dr. Trompeter is lead of the Paediatric Red Cell Service at UCLH and current Chair of the Joint Red Cell Unit Haemoglobinopathy Network including hospitals: UCLH, Whittington Health, Royal Free London and Luton and Dunstable Hospitals, where she also led the trust through the recent Haemoglobinopathy Peer Review Process. She is involved in research in haemoglobin disorders and transfusion, in particular looking at microvesicles and coagulation in sickle cell disease, stem cell generated blood, efficacy of different transfusion modalities and pathogen inactivated blood.

In her role at NHS Blood and Transplant she is developing an evidence base for transfusion in haemoglobinopathies and is involved in various projects including looking at the feasibility of genotyping donors; the haemoglobinopathy patient genotyping project and is the lead on the National Comparative Audit of Transfusion in sickle cell disease that is currently ongoing. She chairs NHS Blood and Transplant’s Haemoglobinopathy Strategy Group and represents NHS Blood and Transplant on the CRG.
Prof. LÉON TSHILOLO (MD, PhD) 
Monkole/Centre de Formation et d’Appui Sanitaire (CEFA), Kinshasa, DR Congo

Léon Tshilolo graduated in medicine in 1980 from University of Padua, Italy and completed his post graduate fellowship in paediatrics in 1984 after Pediatric Residency Training in the pediatric hematology department. He went to Belgium (Institut St Léopold, Antwerpen) where he graduated in Human and Animal Mycology and in Tropical Medicine before his return to his birthplace Lubumbashi, DRC in 1985.

In DRC he implemented a unit of haematology in the Gecamines Medical Department (Kolwezi and Lubumbashi) and established the first comprehensive sickle cell center in the Katanga province. From 1995 to 1997 he used his skills to train in haematology and chemistry at Erasme Hospital, ULB in Brussels (F. Vertongen), Hôpital Robert Debré in Paris (J Elion) and Hammersmith Hospital, London/UK (L Luzzato), respectively.

He is a clinician with a wealth of experience in tropical pediatrics and good expertise on sickle cell disease, he was nominated Professor of Pediatrics and Haematology at Lubumbashi University (UL) and at Ufficial University of Mbuji Mayi (UOM) in DRC. He has a PhD in medicine based on studies on genetics, clinical and hematological parameters in Congolese SCA patients. He is also a visiting professor at Campus Bio Medico di Roma, Italy. He is also temporary consultant for WHO due to his expertise in haemoglobinopathies.

Léon Tshilolo was the Medical Director of Centre Hospitalier Monkole (1998-2015) in Kinshasa where he implemented in 2009 the first systematic newborn screening of SCD. He is presently Director of the Educational and Training Center “CEFA" (Centre de Formation et d’Appui sanitaire) in Kinshasa, and runs a regular educational program dedicated to physicians and biologists.

Léon Tshilolo is a Co-founder and the president of the “REDAC“, a network of Sickle Cell Study in Central Africa who develops multicentric studies on SCD in Central Africa. He is also the DRC lead investigator of REACH-Realizing Effectiveness Across Continents with Hydroxyurea.

He is a member of many scientific associations (paediatrics, mycology, haematology) and a reviewer of medical journals. He is a Member of the French National Academy of Medicine (Académie Nationale de Médecine de France).
Dr John Malcolm Walker BSc MBChB MD FRCP | Consultant Cardiologist
University College Hospital London
Founder & Clinical Director, The Hatter Cardiovascular Institute UCLH
Senior Lecturer University College London

Dr Walker attended the University of Birmingham Medical School, graduating with honours in pre-clinical sciences before undertaking training in clinical cardiology at St Thomas’ Hospital, London and at the University of Oxford. In 1987 he was appointed as consultant cardiologist at University College and the Middlesex Hospitals, London, joining one other established cardiologist.

With the help of a grateful patient, the Hatter Cardiovascular Institute (HCI) was established by Dr Walker in 1989. The Institute now has more than 20 researchers and publishes widely on myocardial protection. Research is undertaken which extends from basic laboratory investigations to international clinical translational research studies.

Dr Walker has developed specific areas of interest within clinical cardiology, including the Cardiovascular Health and Rehabilitation Service within the Hatter Cardiovascular Institute premises. He was also treasurer and president of the British Association of Cardiovascular Rehabilitation from 1999 to 2006. Since 1989 he has investigated the cardiovascular consequences of inherited disorders of haemoglobin and established a unique clinical cardiology service for patients with thalassaemia and sickle cell anaemia. In co-operation with Dudley Pennell at the Brompton Hospital he developed the now accepted methodology of measuring myocardial iron content using magnetic resonance imaging (cMR T2*); he also undertook the first randomised placebo controlled treatment trial in thalassaemia. These efforts have been credited with helping to change the outlook for these patients, with a recorded >70% fall in mortality over the last decade.

Dr Walker served as a scientific consultant and council member for the Thalassaemia International Federation (TIF) and the UKTS. He has published more than 60 articles in scientific journals and lectured all over the world on the topics of myocardial iron overload and the cardiovascular consequences of thalassaemia and sickle cell anaemia. He is the chair of the Data Monitoring Committee for a NIHR sponsored multi-centre study of Atrial Fibrillation and he serves on two Charitable Trust boards.

Neill Westerdale (MSc, RGN, RSCN, RN) | Guy’s and St Thomas’ NHS Foundation Trust

Neill qualified as a general nurse 1987 and as a paediatric nurse in 1989. Neill worked as a paediatric nurse prior to working for GSTT, he had previously managed children affected by sickle cell disease and thalassaemia in an East London children’s hospital. Currently Neill is an advanced nurse practitioner in adult haemoglobinopathies at Guy’s and St Thomas’ NHS Foundation Trust (GSTT). Neill has worked at GSTT since 1994, during this time he has developed a special interest in obstetric management of patients with haemoglobinopathies, pain management and priapism. Currently Neill is also the UK Forum on Haemoglobin Disorders acute nurse specialist representative. Neill teaches both nationally and locally on nursing issues in SCD including pain management, blood transfusion and acute and chronic complications. Neill has written for nursing publications on psychological and transition issues in SCD, as well as the nursing management of adult and paediatric SCD patients.
Dr Winfred Wang | Member
Department of Hematology, St. Jude Children’s Research Hospital

Dr Wang trained at the University of California, Berkeley (BA, Chemistry); University of Chicago (MD); Montefiore Hospital and Medical Center, Bronx, NY and Kauikeolani Children’s Hospital, Honolulu, HI (pediatric residency); University of California Medical Center, San Francisco (pediatric hematology fellowship).

Dr. Wang has provided clinical care for children with non-malignant haematologic conditions for more than 39 years and has been an attending physician at St. Jude Children’s Research Hospital and LeBonheur Children’s Medical Center for the past 35 years. His major interests are clinical care of children with sickle cell disease and bone marrow failure disorders and clinical research in those areas. Most of his clinical research efforts are related to the use of hydroxyurea and the evaluation of the central nervous system in different populations of children with sickle cell disease. He was formerly the leader of the St. Jude Comprehensive Sickle Cell Center and the BABY HUG multi-center trial. In 2015, he received the Distinguished Career Award from the American Society of Pediatric Hematology/Oncology.

Other current appointments are Professor, Dept. of Pediatrics, University of Tennessee Center for the Health Sciences and Attending Physician, LeBonheur Children’s Medical Center.

Professor Ambroise Wonkam | Division of Human Genetics, Faculty of Health Sciences, University of Cape Town, Cape Town, Republic of South Africa

Prof Ambroise Wonkam is a specialist medical geneticist, associate professor/senior consultant in the Division of Human Genetics, Faculty of Health Sciences, and University of Cape Town, South Africa. After MD training from the Faculty of Medicine and Biomedical Sciences, University of Yaoundé I (Cameroon), Dr Wonkam completed a thesis in cell biology in the department of morphology, University of Geneva (Switzerland) and a PhD in human genetics, University of Cape Town, South Africa. He was awarded the 2003 Denber-Pinard Prize for the best thesis from the Faculty of Medicine, University of Geneva. Other salient aspects of Dr Wonkam’s background include his education as a medical geneticist at a highly reputable genetics department in Geneva (Switzerland). He subsequently practices medical genetics in both European and African contexts.

Prof Wonkam’s interests are reflected in more than 70 peer-reviewed publications, which are in molecular, clinical educational and ethical aspects of medical genetics. His major research focuses on disease of Africans including psychosocial burden and genomics modifiers of sickle cell disease (SCD); genetics of hearing loss among Africans and other various monogenic conditions of the people of African descent. Prof Wonkam recently won the very competitive Clinical Genetics Society International Award for 2014 from the British Society of Genetic Medicine.

Prof Wonkam is secretary of the African Society of Human Genetics, board member of the International Federation of Human Genetics Societies and council member of the Human Genome Organization. He is also member of the steering committee of H3Africa consortium, leading specifically the SCD project.
Abstracts

Day 1

Wednesday 7 October 2015
PLENARY SESSION

Overview of Sickle Cell Disease and Treatment Options

Dr Baba Inusa

Sickle cell disease is most prevalent in Sub-Saharan Africa, Caribbean, Middle East, India and a growing problem in Europe, America. While Sub-Saharan Africa accounts for over 2/3rd of the burden of disease the prevalence is estimated at 70-100,000 in the USA and 15,000 in the UK. In the UK over 70% patients with SCD live in greater London. It is estimated that 100,000-150,000 new babies with SCD are born in Nigeria. WE will describe methods of estimating the burden of disease based on the frequency of sickle cell trait.

This makes SCD as the leading genetic disorder in the UK and therefore requires increasing emphasis in understanding the pathology, presentation and management and updates about new research and new therapies. The life span of sickle cell disease varies considerably across the different parts of the world. Recent advances in management may not be available for patients living in developing countries where the numbers are high and the resources are limited. Other issues are universal including myths, and challenge of transition planning.

The aim of this presentation is to define the sickle cell syndrome and discuss the common presentations in childhood and adult. The cardinal feature of SCD is pain, therefore would discuss the case for adequate pain management and adjunctive therapies in sickle cell disease. Hydroxyurea is currently the only approved drug in modifying SCD. This is reflected in the reduction of hospital admission in various Hydroxyurea studies. Further discussion will address the frequency of end organ damage such as stroke (11% by 18 years, 35% Silent cerebral infarct lesion at 15yrs and 45% life time risk of over stroke); end stage renal failure 11% by aged 37 years. We will discuss stroke prevention in SCA and the role of abnormal transcranial Doppler scanning; the role of blood transfusion and the question about hydroxurea use. Reference will be made to number speakers who would discuss the various teams raised.

Recommendation would be made with regards to key interventions in therapy and presentation. Current UK / USA management guidelines will be mentioned especially with regards to Penicillin prophylaxis, Immunisations and acute management of in emergency department. To address the challenge of diagnosis, therapeutic interventions and lack specialist centres to manage patients in a planned manner especially when the numbers are overwhelming. Prospects for the future as a result of individual efforts and state funded programmes
The pathology and pathogenesis of sickle cell disease in man is mainly studied at autopsy, since the critical organs that are damaged are not biopsied in clinical case work. The fundamental process is the interaction of sickled red cells with endothelium: in small vessels, this leads to classical sickled cell microvascular obstruction and distal ischaemia/hypoxia, leading to infarction of tissues; in glomeruli, it leads to progressive sclerosis (and renal failure); in larger arteries, it leads to progressive intimal thickening and chronic obstruction and/or weakening of the vessel wall (eg cerebral stroke and haemorrhage; pulmonary hypertension). Splenic infarction is the major risk factor for overwhelming infections. With better management of sickle disease, patients live longer and the patterns of critical pathology change; eg, we see increasing numbers of pulmonary arteriopathy with right heart failure causing death.
Assessment and management of iron overload in – thalassaemia major patients during the 21st century: a real-life experience from the Italian WEBTHAL project.

Professor Antonio Piga

Department of Clinical and Biological Sciences, Turin University, Italy.

The use of disease specific clinical records, as WEBTHAL for thalassemia, allows a proper storing daily routine for high quality longitudinal follow-up of individual patients and series. Sharing data among centers allows the analysis of large amount of data with meaningful epidemiological value. Here is a published example.¹

We conducted a cross-sectional study on 924 – thalassaemia major patients (mean age 30·1 years) treated at nine Italian centres using the WEBTHAL software, to evaluate real-life application of iron overload assessment and management standards. Serum ferritin <2500 ng/ml was a risk factor for never having liver iron concentration (LIC) measurement, while absence of cardiac disease and siderosis were risk factors for a delay in LIC measurement >2 years. Patients who never had a cardiac MRI (CMR) T2* measurement were <18 years, had iron intake ≤0·4 mg/kg per day, or a serum ferritin <2500 ng/ml. A history of normal CMR T2* was the main risk factor for a delay in subsequent assessment of >2 years.

Deferoxamine (22·8%) was more commonly used in patients with Hepatitis C Virus or high serum creatinine. Deferiprone (20·6%) was less commonly prescribed in patients with elevated alanine aminotransferase; while a deferoxamine + deferiprone combination (17·9%) was more commonly used in those with heart disease or high iron intake. These observations largely echoed guidelines at the time, although some practices are expected to change in light of evolving evidence.

Management of sickle cell disease (SCD) in Africa needs to be accompanied by various preventive strategies, including early detection via prenatal genetic diagnosis (PND). Contrary to Cameroonian doctors who considered termination of an affected pregnancy (TAP) for SCD in 36.1%, the majority of parents (62.5%) with affected children accepted TAP in principle. In practice, most women opted for TAP (90%), justified by a huge psycho-social burden. The ethical and legal challenges of PND prompted the need to explore the use of genetics for secondary prevention of SCD. In 610 Cameroonian SCD patients, the genomic variations in two principal foetal haemoglobin-promoting loci were significantly associated with foetal haemoglobin levels. In addition, the co-inheritance of a 3.7-kb α-globin gene deletion and SCD was associated with a late disease onset and possibly improved survival: there was a much higher allele frequency of the 3.7-kb α-globin gene deletion in SCD patients (40%) than in haemoglobin AA controls (10%). The data indicate the urgent need to develop and implement policy actions in sub-Saharan Africa on at least four levels: (1) the implementation of SCD screening practices and early neonatal follow-up; (2) the development and incorporating of socio-economic support to alleviate the burden of SCD on affected families; (3) the exploration of the appropriateness of the medical abortion laws for SCD, and (4) the development of national plans for genetic medicine, including research on genomic variants that affect the phenotypes of SCD, in order to potentially use them for anticipatory guidance.


1 Division of Human Genetics, Faculty of Health Sciences, University of Cape Town, Cape Town, Republic of South Africa.
Environmental causes of variability in Sickle Cell Disease

Professor David Rees

Sickle cell disease (SCD) is a severe condition with acute and chronic complications. Median life expectancy is reduced by a minimum of 30 years in all countries, with much greater reductions in low-income countries. The severity is widely variable, with some having no symptoms and others frequent, life-changing complications. Most of this variability is unexplained by genetic factors. Environmental factors, including climate, air quality, socioeconomics, exercise and infection, are likely to be important, as demonstrated by the stark differences in outcomes between patients in Africa and USA/Europe. The link between cold weather and acute pain in SCD is poorly understood and variable. Although most studies show that exposure to cold or wind increases hospital attendance with acute pain, these effects seem to vary with geography. Air pollutants intercorrelate closely, and increasing overall levels seem to correlate with increased hospital attendance, although higher levels of carbon monoxide may offer some benefit. Exercise causes adverse physiological changes, although this has not been linked to clinical complications, this may be off-set by improvements in cardiovascular health. Most SCD patients live in low-income countries and socioeconomic factors are important, but little studied beyond documenting that SCD is associated with decreases in social status. All the above factors are likely to be central to the pathology and variability of SCD, and large prospective studies are needed to understand these effects better.
Genetic determinants of severity

Stephan Menzel, MD

While sickle cell disease seems, superficially, to be a genetically simple condition, anyone working with sickle patients is aware that this disease is far from simple, displaying significant heterogeneity and complexity. At least part of the clinical diversity appears to be constitutional, i.e. genetically determined, and a network of underlying genetic modifier genes is presently emerging.

Beyond the first level of genetic complexity, arising from co-inheritance of other globin gene mutations, genetic modifiers of HbF persistence have been shown to have significant influence. Historically, these have been divided into factors linked to the sickle mutation and and those ‘unkinked’ to it. This division has become less meaningful in the light of new insight from population-genetic and biological studies: factors residing inside the beta globin cluster on chromosome 11 are less strongly linked to the sickle allele as previously thought and effects arising from other chromosomes can appear to be linked to the beta globin genes, due to population effects. An example for the latter is the ‘Arab/Indian’ somewhat milder sickle phenotype, which was thought to be due to variants within the beta globin cluster, but which is likely partially caused by MYB enhancer variants (HMIP-2) on chromosome 6, which have a high frequency in Middle Eastern and Indian populations.

Currently, the first studies evaluating the interaction of the genetic HbF modifiers with the efficacy of hydroxyurea therapy are being conducted. Again, ethnic effects are likely to muddy the waters unless they are carefully evaluated during the investigation.

Genetic studies of sickle cell disease are intriguing, not least because the condition has been, and is still changing, along with environmental pressures and the movement of human populations. The well-known malaria-protective effect of sickle carrier status has shaped disease prevalence and appearance in the past. Today, population migration and integration are changing the appearance of sickle cell disease, especially in countries where significant parts of the African diaspora are residing. There the sickle mutation is found on very diverse, African and non-African genetic backgrounds, occasionally resulting in new forms of the disease, with potentially distinct clinical profiles.

With the availability of increasingly sophisticated genetic tools, large patient study cohorts and a better understanding of human populations, another chapter of our knowledge of sickle cell disease genetics is about to be opened. Once we understand why some patients have genetically mild disease, we might be able to derive new forms of treatment, using pharmaceutical or gene-therapeutical approaches.
Biomarkers of severity in SCD

Dr Valentine Brousse

Reference Centre for Sickle Cell Disease, Paediatric Department, Hôpital Universitaire Necker Enfants Malades, APHP, Paris; Université Paris Descartes, Paris; INSERM, U1134, F-75739 Paris, France; Université Paris Diderot, Sorbonne Paris Cité, UMR_S 1134, F-75739 Paris, France; Institut National de la Transfusion Sanguine, F-75739 Paris, France; Laboratoire d’Excellence GR-Ex, France

Sickle cell disease is characterised by a highly variable phenotypic expression both in time and within patients ranging from mild asymptomatic haemolytic anaemia to acute, recurrent, and sometimes fatal organ or systemic complications. Contrasting with a straightforward and long described single point mutation, multiple downstream-interrelated mechanisms are responsible for disease expression and pathophysiology. Numerous blood and urine biomarkers have been described in an attempt to screen for organ damage or monitor therapeutic intervention or more generally to predict disease severity. However, up to date, no biomarker has been identified to reliably fulfil any of those conditions.

This talk will review the most studied biomarkers in SCD in relation with pathophysiology: haemoglobin F levels, adhesion molecules notably CD36, α4β1, Lu/BCAM, biomarkers of haemolysis (reticulocytes, LDH, free haemoglobin) biomarkers of oxidative stress, biomarkers of vasculopathy and endothelial dysfunction (circulating endothelial cells, Endothelin-1, vascular endothelial growth factor).

Results of a longitudinal infant cohort prospective study will be presented, based on the expression pattern analysis of 9 adhesion molecules on red blood cells. Comparing 54 asymptomatic SCA and 17 non-SCA very young infants of comparable age (median 144 days, 81-196) we showed that haemoglobin F (HbF) level was unsurprisingly elevated in SCA infants (41.2% ± 11.2) and 2-4 fold higher than in non-SCA infants, yet SCA infants presented significantly decreased Hb level and increased reticulocytosis. Cytometry analysis evidenced a specific expression profile on reticulocytes of SCA infants, with notably an increased expression of the adhesion molecules Lu/BCAM, ICAM-4 and LFA-3, both in percentage of positive cells and in surface density. No significant difference was found on mature red cells at this very young age.

Further analysis of this same cohort studied at 24 months showed that the subpopulation of Lu/BCAM positive reticulocytes circulating early in life was stable over time despite total elevation of reticulocytes. Circulating mature red cells reflecting the aging of this stress subpopulation displayed a marked increase in Lu/BCAM surface density. Likewise, adhesion analysis using a dynamic adhesion platform showed a steady increase in adhesion along with age of SCA RBCs on laminin, the extracellular matrix ligand of Lu/BCAM.

These results altogether indicate a potential discriminating tool based on adhesion molecules profile, yet to be applicable in clinical routine care.
Morphology remains the basic foundation rung of diagnostics in haematology, even in an advanced era of SNP arrays and whole genome sequencing.

This mini-morphology quiz is an eclectic mix of some basic haemoglobinopathy cases and a few rare, but clinically relevant, case vignettes.

The aim is to reiterate that amalgamating morphology with clinical commentary and indices enables an astute haematologist to formulate a full proof investigative algorithm to crack the diagnosis, however difficult and rare it may be!
Haemoglobin Switching

Dr Noémi Roy

Academic Clinical Lecturer, Molecular Haematology Unit, Oxford University

Natural variations in levels of fetal haemoglobin (HbF) in the context of haemoglobinopathies can alter the phenotype, with high expression of HbF ameliorating the clinical course of both sickle cell disease and thalassaemia1. Therapies aimed at increasing HbF rely on delaying or reversing the natural “switch” from HbF to HbA which occurs perinatally. The design of rational therapies critically depends on our understanding of how this switching mechanism operates. The aim of this session is to review the current understanding of the molecular mechanisms involved in haemoglobin switching. The session will focus initially on normal aspects of gene regulation and silencing, describe the current understanding of haemoglobin switching, and finally review which therapeutic strategies are and will be available to increase HbF levels.

The regulation of gene expression is dependent on genetic factors (eg. promoters, enhancers), as well as epigenetic ones (eg. DNA methylation, histone modifications). The β-globin locus is situated on chromosome 11 and contains all the β-like genes (ε, γ, δ, β) arranged in the order in which they are expressed. Upstream of this region is the locus control region, a set of 5 enhancers containing sequences which target transcription factors (TFs) to ensure high level gene expression in a time and tissue appropriate manner. During fetal life, the enhancers physically interact with β-globin, while after the switch they physically contact β-globin. Histones, which make up the nucleosomes around which DNA is wound, have the ability to be covalently modified and thus provide an epigenetic layer of control, rendering the associated DNA either “open” for gene expression or “closed”, when genes are silenced. Meanwhile, DNA methylation is associated with “closed” chromatin. The γ locus is “open” during fetal life and “closed” during adult life. Drugs which alter DNA methylation (azacitadine/decitabine) and histone modifications (vorinostat/panobinostat) modestly increase HbF and ameliorate the phenotype, however their safety profile in SCD patients is still being evaluated in clinical trials2.

One of the key determinants of haemoglobin switching was identified from GWAS studies evaluating the association between genome-wide SNPs (natural variations in DNA sequence) and natural variations in HbF. Two loci apart from the – globin cluster itself were identified as affecting HbF levels, one of which is BCL11A3. This zinc finger TF’s expression levels are low during fetal life and rise correspondingly to the silencing of β-globin and the induction of β-globin. BCL11A works in a large multi-protein complex with known gene silencers. Natural variations in BCL11A expression mirror HbF levels, and mouse studies have confirmed that disruption of BCL11A abolishes/retards the expression of HbA, keeping HbF as the main haemoglobin. While BCL11A may seem an attractive target for novel drugs, its importance in non-erythroid cells and the known lethality of mice in which BCL11A is completely abolished, render this a poor target4. However, a recent advance using the novel approach of CRISPR/Cas9 technology has come to light. The expression of BCL11A itself is controlled by an enhancer. Natural variants in that region decrease the total amount of BCL11A produced and are associated with mild increases in HbF. In vitro studies have now shown that CRISPR/Cas9 disruption of the BCL11A enhancer region abolishes BCL11A expression and increased HbF levels 4-fold. This paves the way for genome editing strategies whereby HSCs could be harvested, genome-edited ex vivo to disrupt the BCL11A enhancer, and transplanted back to patients in an autologous fashion to ensure high HbF expression, and consequent amelioration of their phenotype.

References

The presentation includes an overview of the laboratory diagnosis of haemoglobinopathies including haemoglobin structure, inheritance and the types and proportions of haemoglobins found at birth and in adults. The routine diagnostic techniques available will be reviewed and some of the limitations highlighted. Diagnostic algorithms for alpha and beta thalassaemia trait as well as the common haemoglobin variants are well established and will be reviewed, with the use of high performance liquid chromatography (HPLC) plots where appropriate. HPLC plots highlighting diagnostic difficulties, including differentiating the various sickling disorders, will be shown and discussed. Other frequently raised issues associated with differentiating alpha zero and alpha plus thalassaemia and beta thalassaemia with borderline Hb A2 and will also be discussed.

Relevant guidelines include:


Molecular Diagnostics in haemoglobinopathies

Dr Mary Petrou

Haemoglobinopathy Genetics Centre
University College London, Institute of Women’s Health and University College London Hospitals NHS Foundation Trust, 86-96 Chenies Mews London WC1E 6HX. United Kingdom.

This seems a good time to reflect on the enormous changes that have taken place in the field of genomics. The Human Genome Project, an important feature in the molecular revolution, involved an international effort to create an ordered map of the human genome and make it available worldwide. The HGP was completed in 2003 and the detailed knowledge of the human genome provides new avenues for advances in medicine and biotechnology. It spurred a revolution in biotechnology around the world. These advances will touch the lives of many but what is the fate for low resource countries?

There were already existing genomic advances that were known before the start of The Human Genome Project, such is the case for thalassaemia and sickle cell. We knew the genes and the mutations, the mechanism of loss of function, yet we do little for the majority of the patients. We know the mutations that cause thalassaemia and sickle cell, there is reliable technology for carrier detection and molecular technology for prenatal diagnosis but it is little used in many countries where the incidence of sickle cell and thalassaemia is high and the populations are large, or where used in these countries it has little effect in reducing the huge number of affected children born.

The HGP invested large sums of funds to address the ethical, legal and social issues (ELSI) that arose from the project. However major ELSI issues have not been addressed, such as the inability of the knowledge acquired to be translated for the benefit of developing countries, how to provide optimum services to patients and how the existing technology can be used to provide prevention programmes for countries such as Africa, India, Pakistan, Bangladesh, Central Asia, and South East Asia, countries where the incidence of thalassaemia and sickle cell is significant. The ultimate goal; to provide a truly informed choice for couples at risk for thalassaemia and sickle cell disorders and optimal services for patients affected by these disorders.

Which are the right diagnostic methods for countries? Can we employ suitable strategies for all countries that will provide reliable results and reduce the burden?
Evaluation of Severity of Painful Sickle Cell Crises with oral PGLG Treatment

Charles Stark

Background
Based on our work in the mid 1990’s, our laboratory described the role of L-glutamine as one of the precursors to nicotinamide adenine dinucleotide (NAD) production in sickled Red Blood Cells to counter oxidative stress. We hypothesized that oral administration of L-glutamine would decrease the incidence of painful sickle cell crises (PSCC). Our multi-center Phase 2 placebo-controlled trial utilizing oral pharmaceutical grade L-glutamine (PGLG) in Sickle Cell Disease (SCD) suggested benefit when measuring PSCC incidence. Subsequently, a multi-center Phase 3 trial further supported the outcome of our Phase 2 trial. We are currently reporting our evaluation of the total number of patients categorized into “None”, “Mild”, “Moderate”, and “Severe” between the treatment arms from our Phase 3 study.

Methods
A randomized, double-blind, placebo-controlled, parallel-group Phase 3 study was conducted at 31 sites in the United States. Patients that were 5 years of age and older with at least 2 PSCCs during the year prior to enrollment were randomized by stratifying for hydroxyurea use during the study. Dosage of PGLG or Placebo powder formulation was 0.3 grams per kilogram body weight given orally twice daily for 48 weeks. The primary endpoint for the trial was to evaluate the difference in the number of PSCC events between treatment arms where events were adjudicated by a blinded third party committee. Investigators ranked PSCC severity as, “Mild” (1), “Moderate” (2) and “Severe” (3). For analysis, patients without crises were ranked as “None” (0) and the difference between treatment arms was evaluated using Cochran Mantel Haenszel (CMH) Ranked Scores statistics. Each patient was counted only once at the highest level of severity.

Results
A total of 230 subjects were enrolled; ages 5-58; 53.9 % female; randomization was 2:1 where 152 patients were assigned to L-glutamine and 78 to placebo. The groups were well balanced for baseline clinical characteristics. The comparison of severity for PGLG vs. Placebo indicated that “None” (0) was 24% vs. 10% respectively; “Mild” (1) was 6% vs. 8%; “Moderate” (2) was 36% vs. 35%; and “Severe” (3) was 34% vs. 47%. Summary statistic for the cohort taken as a whole indicated a treatment difference between groups (p = 0.0167).

Conclusion
PGLG therapy may provide clinical benefit over placebo in some adult and pediatric patients with a history of two or more crises per year. Difference between treatment arms appeared to be driven by patients without PSCC events “None” (0) and by a decrease in “Severe” (3) PSCC events.
The Cardiomyopathy of Sickle Cell Disease

Associate Professor Charles Quinn

Sickle cell disease (SCD) causes progressive cardiopulmonary morbidity, beginning in childhood, which can ultimately be fatal. As a group, cardiopulmonary complications such as acute chest syndrome and sudden death are now the most common causes of death in SCD, especially in adolescents and adults. Patients with SCD have features of both an anemia-related, high cardiac output state and a restrictive cardiomyopathy. We propose that this is a unique cardiomyopathy (hyperdynamic-restrictive) that has been overlooked and understudied. Restrictive physiology could explain the modest increases in pulmonary artery pressure in some patients with SCD, as measured by cardiac catheterization or estimated by tricuspid regurgitant jet velocity (TRJV), which has often been attributed to a primary pulmonary arterial hypertension (PAH). Restrictive physiology could also be the cause of unexplained sudden cardiac death in SCD, which is a feature of other forms of restrictive cardiomyopathy with modest elevations of TRJV. Our overarching hypothesis is that increased ROS-mediated AT1R-TGFβ1 signalling is pro-fibrotic which, in combination with vaso-occlusive ischemia-reperfusion injury, results in an age-dependent, progressive, hyperdynamic-restrictive cardiomyopathy. We are currently conducting studies to challenge the prevailing concept of a primary pulmonary vasculopathy in SCD to a cardiomyopathy-centered model with secondary pulmonary vascular changes.
Molecular mechanisms of pain in sickle cell disease

Professor Kalpna Gupta, PhD

Vascular Biology Center, Division of Hematology, Oncology and Transplantation, Department of Medicine, University of Minnesota, Minneapolis, MN.

Sickle cell disease (SCD) is the most common inherited disorder, characterised by recurrent acute pain due to vasoocclusive crises (VOC) superimposed on chronic pain. We examined the contribution of mast cells using genetic and pharmacologic approaches in transgenic sickle mice. We used homozygous BERK sickle mice and control mice expressing normal human hemoglobin A. We found that mast cell degranulation/activation is significantly higher in the skin of sickle mice as compared to controls. This increased mast cell activation contributes to the pathophysiology of SCD by promoting neurogenic inflammation and nociceptor activation via the release of tryptase and substance P in the skin and dorsal root ganglion. Inhibition of mast cells with imatinib in vivo, led to a significant decrease in the release of cytokines from skin biopsies ex-vivo. Importantly, it led to a correlative decrease between GMCSF and white blood cell counts in sickle mice. Mast cell deletion in sickle mice as well as pharmacologic treatment with imatinib led to a decrease in tonic and hypoxia/reoxygenation evoked (simulating VOC) hyperalgesia in sickle mice. Mast cell stabilizer cromolyn sodium reduced chronic hyperalgesia and improved the outcome of relatively lower dose of morphine, which is otherwise ineffective. We conclude that mast cells provide a druggable target to ameliorate sickle pathophysiology and ameliorate pain.
Novel Insights into the Pathogenesis of Acute Chest Syndrome.

Professor Solomon F. Ofori-Acquah, PhD. Division of Hematology/Oncology, Center for Translational and International Hematology, Vascular Medicine Institute, Department of Medicine, University of Pittsburgh, Pittsburgh, USA.

Acute chest syndrome (ACS) is the leading reason for intensive care admissions and a major cause of death in sickle cell disease (SCD). It is diagnosed by the presence of a new pulmonary infiltrate on a chest x-ray in combination with a constellation of many clinical presentations. Although ACS was first described over 40 years ago, the mechanism that is responsible for this lung condition has not been clearly defined. Historically, three common etiological factors have been postulated to cause ACS, namely infection, fat emboli, and infarction. However, in the largest prospective study aimed at identifying the causes and outcome of ACS, none of these factors were identified in nearly fifty percent of patients. Moreover, infection is rarely confirmed in adult ACS patients who incidentally develop a more severe form of the condition that is associated with a 4-fold higher mortality rate than in children. Regardless of age, a diagnosis of ACS is typically associated with acute anemia characterized by intravascular hemolysis, and moreover the degree of anemia is predictive of death. Based on these observations, we have proposed a new model of ACS pathogenesis; the heme hypothesis, which posits that excess extracellular heme generated during acute illness in SCD patients trigger ACS. Clinical, genomics and experimental data in transgenic SCD mice support this new model of ACS pathogenesis. Moreover, emerging data from other disease models show that excess extracellular heme promotes the development of acute lung injury. This plenary lecture will discuss the basic principles of the heme hypothesis and the clinical and experimental findings that support this new paradigm of ACS pathogenesis.
Abstracts
Day 2
Thursday 8 October 2015
PLENARY SESSION

Iron chelation in children with haemoglobinopathies

Dr Banu Kaya
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Children with haemoglobinopathies, mostly those requiring transfusion therapy, can develop significant iron loading. End organ damage from cumulative iron overload often occurs from the second decade onwards but some children exhibit organ dysfunction from a very young age. This is a challenging situation because iron overload induced damage which may have started in very early childhood may not manifest itself clinically until later life, and investigations to monitor iron loading and tests of organ function are not always organised in young children. An example of this includes hypogonadism where tests of pituitary gonadal function are difficult to assess before the onset of puberty when irreversible damage may have already occurred. With this in mind, the timing of chelation therapy to ideally prevent any iron accumulation as well as avoiding toxicity at low iron burden is important. Good chelation contributes to good outcomes. There is now increasing evidence to support choice of chelation in children. Close monitoring for response and toxicity, optimal dose adjustment and a proactive approach to individualising care is important to support effective chelation. The practical aspects of chelation management involve a multifaceted holistic approach with multidisciplinary support and education to instil independence and self-care.
Endocrine and bone complications in β-thalassaemia: current understanding and treatment.

Associate Professor Antonis Kattamis

Prevalence of endocrinopathies in patients with thalassaemia, even though it varies in different populations, is high. The pathogenetic mechanism for the development of endocrinopathies is multifactorial. Main contributing factors are chronic anaemia, iron overload and toxicity from the therapy.

Iron overload seems to be the most significant factor and the main one that can be treated. Recent MRI studies have shown that iron deposition starts very early in transfusion history. The development of iron overload seems to parallel between endocrine glands and other organs, like the heart.

Some endocrine anomalies like growth and hypogonadism manifest in young patients while others, like bone disease, progress with age.

Growth in patients with thalassaemia, even though much improved with regular transfusion therapy, remains suboptimal in many patients. Aggressive iron chelation with desferrioxamine in low iron overload levels had led to significant bone toxicity and growth abnormalities. This adverse event is no longer observed with current iron chelation protocols. Hypogonadism is commonly observed in patients with severe iron overload and it is mainly due to pituitary deficiency. Disturbances of glucose metabolism and diabetes are common complications of thalassaemias related mainly to transfusional hemosiderosis. They usually appear during the second decade of life; their incidence increases with age and severe hemosiderosis. Abnormalities on glucose metabolism are diagnosed using criteria related to the results of the oral glucose tolerance test. Diabetes resembles more to type II diabetes with main differences the age of onset and the slow progression of disturbances of glucose metabolism and insulin secretion.

Thyroid dysfunction is also commonly observed and can be either of central or peripheral aetiology.

Bone disease increases dramatically with age and it may affect quality of life of the patients. Pathophysiology for the development of bone disease is complex. A stepwise therapeutic approach is proposed, especially for patients with progressive symptomatology.

The main goals of optimal therapy in thalassaemia are focused in treating chronic anaemia with transfusions, in preventing iron accumulation and iron-induced toxicity and in preventing and treating toxicity from chronic therapy. Close monitoring for the development of endocrinopathies and of bone disease is an essential part of optimal therapy, as timely intervention, like intensification of iron chelation therapy, may actually reverse these complications.
Guidelines for diagnosis and management of Beta-thalassemia intermedia

Professor Ali Taher, MD, PhD, FRCP

Thalassemia intermedia (β-TI) is one of the three most common subtypes of the non-transfusion-dependent thalassemias (NTDT). NTDT refers to patients with a genetic defect or combination of defects that affect hemoglobin (Hb) chain synthesis, and consequently, the oxygen-carrying capacity of red blood cells (RBCs).

The diagnosis of NTDT can be made by using simple lab tests (complete blood count (CBC) showing red cells with decreased cell size, reflected by a low mean corpuscular volume (MCV) and low hemoglobin content, reflected by a low MCH) or, more conclusively, using DNA molecular techniques. Ultimately, NTDT remains a clinical diagnosis where both the physician's clinical sense and the patient's clinical picture are integral to reach a diagnosis.

The pathophysiology of β-TI is determined by three main factors: ineffective erythropoiesis, chronic anemia, and iron overload. Ineffective erythropoiesis and hemolysis lead to chronic anemia and hypoxia, with subsequent erythroid marrow expansion and complications such as hepatosplenomegaly, extramedullary hematopoietic pseudotumors, bone deformities and osteoporosis. More importantly, ineffective erythropoiesis and hemolysis are associated with hypercoagulability, attributed to the thrombogenicity of hemolyzed red blood cells, ultimately leading to a high incidence of thromboembolic and cerebrovascular events, as well as pulmonary hypertension. Furthermore, ineffective erythropoiesis and chronic anemia lead to hepcidin suppression by erythroid factors, increased iron absorption from the gut and increased release of recycled iron from the reticuloendothelial system (RES); all culminating in non-transfusional iron overload, mainly in the liver and less so in the heart. Without treatment, iron in NTDT patients continues to accumulate and a considerable proportion of NTDT patients eventually reach liver iron concentrations (LIC) thresholds of clinical significance, with most iron-related morbidity appearing beyond 10 years of age. LIC levels ≥5 mg Fe/g dry weight (dw) are associated with considerable morbidity risk increase. A recent longitudinal 10-year follow-up study showed a SF level of ≥800 ng/ml to be the threshold after which morbidity risk develops.

Management of NTDT involves four main principles: transfusions, splenectomy, HbF induction and iron chelation. Transfusion therapy may be an important part of management particularly in cases of acute stress, to support growth and development in childhood, or to prevent clinical morbidities stemming from ineffective erythropoiesis or hemolytic anemia. As for splenectomy, although it is associated with improvements in hemoglobin levels, it leads to several short- and long-term adverse events, warranting extreme caution in deciding on when to splenectomize patients. Fetal hemoglobin induction therapy has been evaluated in non-randomized studies, with benefits extending beyond hematologic improvements to lowering morbidity risk. Finally, iron chelation therapy is currently an important cornerstone of managing NTDT patients with iron overload and minimizing disease related complications.

New modalities that aim to ameliorate ineffective erythropoiesis or address iron dysregulation are currently under development including JAK2 inhibitors, minihepcidins, as well as Sotatercept (ACE-011) and Luspatercept (ACE-536).

Optimal management of NTDT patients requires a holistic approach targeting all hallmarks of the disease to ensure favorable patient outcomes.
References


Body Image and Depressive symptoms in Jamaican Adolescents with Sickle Cell Disease

Komal Bhatt-Polouse

Introduction
In adolescence, numerous physical and mental changes occur and therefore body image perception can have a huge psychosocial impact. It can be even more challenging for an adolescent with a chronic illness for example Sickle Cell Disease (SCD), especially since it has been shown that puberty in SCD is often delayed.

Aims & Objectives
The aim of this study is to examine the association of body image perceptions with symptoms of depression in Jamaican adolescents with SCD.

The objectives are as follows
To determine the body image perception of Jamaican adolescents with and without SCD
To determine the relationship between desired body image and gender in Jamaican adolescents with and without SCD
To determine the depressive symptom score in Jamaican adolescents with and without SCD
To examine the association between body image perception and depressive symptoms in Jamaican adolescents with and without SCD.

Method
The study was a secondary analysis of data collected on adolescents at the Sickle Cell Unit (SCU) in Kingston, Jamaica over a 6 month period (a cross-sectional study) as well as data from the Jamaican Youth Risk and Resiliency Behaviour Survey (JYRRS) in 2006 (a national survey collected using cluster sampling). A questionnaire derived from the JYRRS study was administered to adolescents with SCD to examine body image perceptions and depressive symptoms and comparisons between both groups were made.

Results
Approximately 55% of adolescents with SCD and 52% of adolescents in the national sample (JYRRS) perceived their body image to be normal. In SCD adolescents, males as compared to females desired a larger body silhouette (27.7% vs. 6.0%; p: 0.001) whereas females as compared to males desired a thinner body silhouette (32.8% vs. 10.6%; p value: 0.001). In the National sample, females, when compared to males, desired a thinner body silhouette (33.1% vs. 21.5%; p value<0.001). Depressive symptom scores were low for both groups (2.46±1.93 for SCD group) and (1.90±1.87 for non-SCD group), but adolescents with SCD had significantly higher scores (p=0.018). In a multinomial regression model, controlling for SCD status, adolescents with depressive symptoms ≥ 4 were 56% more likely to perceive themselves as overweight. Given the greater body dissatisfaction among Jamaican adolescents with SCD, special attention is warranted to address their body image perception. Health care providers also need to ensure screening for depression is regularly conducted on Jamaican adolescents with SCD.

References
K. Bhatt-Polouse, M. Asnani, A. Harrison, M. Reid, K. James;
The University of the West Indies (UWI), October 2014 (Unpublished)
Quality of Life in Sickle Cell Disease

Dr Jerlym Porter

Background
Pediatric patients with sickle cell disease (SCD) are at risk for poor health-related quality of life (HRQOL). Poor HRQOL has been associated with increased hospitalizations and emergency department visits, disease-related complications, and other medical comorbidities. Most research has focused on caregiver-report of HRQOL and non-disease specific measures. Furthermore, there is a lack of research examining HRQOL and associations with psychosocial factors such as emotional and behavioral functioning, family functioning and perceived stressors.

Aims & Objectives
The objectives of this study were to 1) describe HRQOL of children with SCD as reported by the caregiver and the child, 2) compare the relationship between caregiver and child report, and 3) determine psychosocial predictors of child-reported HRQOL.

Methods
Participants were recruited from a children's research hospital for a larger study examining nocturnal enuresis among patients with SCD. Demographic information included age, gender, and disease severity. HRQOL was assessed with the PedsQL™ Generic Core Scales, PedsQL™ Multidimensional Fatigue Scale, and PedsQL™ SCD Module. Emotional and behavioral functioning was assessed with the Behavior Assessment System for Children, Second Edition. Family functioning was assessed with the McMaster Family Assessment Device. History of stressful life events was assessed with the Life Events Scale. Correlation analyses were conducted for continuous variables and independent t-tests were conducted for continuous and categorical variables. Paired t-tests were used to calculate the difference between mean scores of the child and caregiver for each caregiver-child pair. Hierarchical multiple regression was performed to investigate whether psychosocial factors predicted child-reported HRQOL, after controlling for demographic factors.

Results/Conclusions
The sample consisted of 171 patients with SCD aged 6-17 years (Mean age = 11.53, SD = 3.52; 50.3% female). Genotypes included 58.5% HbSS, 26.9% HbSC, 7.6 HbSβ+ thalassemia, 7.0% HbSβ0 thalassemia. Caregivers and children rated generic core HRQOL similarly; however, overall caregivers rated their child's fatigue and SCD HRQOL better compared to child-report. Caregivers reported significantly lower sleep/rest fatigue and overall fatigue scores compared to child report. Caregivers reported significantly better HRQOL compared to child report for all SCD HRQOL and all subdomains except pain and hurt, pain management, and communication I. Hierarchical regression analyses revealed that child-reported psychosocial HRQOL was predicted by inattention/hyperactivity (β= -.28, p=.019) and personal adjustment scores (β= .28, p=0.034) and to a lesser extent, stressful life events (β= -.23, p=0.04) after controlling for demographics. Child-reported family affective responsiveness (β= -.25, p=.02) significantly predicted child-reported physical HRQOL, after controlling for demographics. Child-reported fatigue was largely predicted by inattention/hyperactivity scores (β= -.44, p<.001) and to a lesser extent, stressful life events (β= -.24, p=.028), after controlling for demographics. Caregiver-report of child's adaptive skills significantly predicted child-reported fatigue (β=.29, p=.025) and caregiver-report of child's internalizing problems predicted child-reported SCD HRQOL (β=-.38, p=.004), after controlling for demographics. Results suggest the importance of using both caregiver and child report of HRQOL and psychosocial functioning. Future research exploring underlying attitudes and beliefs that impact HRQOL will promote the tailoring of effective psychosocial interventions for pediatric patients with SCD and their families.

References:
Quality of Life and Quality of Care for Adults with Sickle Cell Disease

Dr Marsha Treadwell

Background: Emotional distress may adversely affect the course and complicate treatment for individuals with sickle cell disease (SCD). We evaluated variables associated with physical and mental components of health-related quality of life (HRQoL) in SCD in the context of a biobehavioral model.

Methods: We conducted a cross-sectional cohort study of 77 adults with SCD (18–69 years; 60% female; 73% Hgb SS) attending an urban, academic medical center. We measured emotional distress (Patient Health Questionnaire–9, Generalized Anxiety Disorder 7-item scale), clinical complications and utilization, barriers to health care, socio-demographics and HRQoL (SF-36 Health Survey). We developed models predictive of physical and mental HRQoL by conducting stepwise regression analyses.

Results: Sample prevalence of moderate to severe depression and anxiety symptoms was 33% and 36%, respectively; prevalence of impaired physical and mental HRQoL was 17% and 16%, respectively. The most common barriers to care included providers with negative attitudes and limited knowledge about SCD; transportation; insurance; social, family and caregiver support; emotional barriers; individual barriers (e.g. memory, health literacy, motivation); and SCD related barriers (e.g. fatigue and pain). Increased symptoms of depression, older age, and ≥ 3 emergency department visits in the previous 12 months were independently associated with lower ratings of physical HRQoL, controlling for anxiety and sex. Increased symptoms of depression were independently associated with lower ratings of mental HRQoL, controlling for barriers to care, insurance status, lifetime complications of SCD, and sex.

Conclusion: Emotional distress is an important contributor to both physical and mental HRQoL for adults with SCD, although socio-demographic variables and barriers to care must also be considered. Innovative approaches that integrate mental health interventions with SCD clinical care are needed.
Pain and quality of life in hospital for adults with sickle cell disease

Dr Kofie A Anie

Acute pain is a hallmark of sickle cell disease for which frequent hospital admissions may be required, affecting the quality of life of patients. More than 90% of hospital admissions of patients with SCD in the UK have been shown to be for acute pain treatment, and the management of acute painful episodes continues to pose a challenge for clinicians.

510 adult inpatient self-assessments of pain, mood, and health related quality of life with health utility (measured on the EQ-5D) across three time points on admission, before discharge, and at one-week follow-up were examined. Results showed that mood and health related quality of life steadily improve with reduction of pain during and after an acute sickle cell pain episode. Moreover, examining health utility in relation to pain during hospital admissions is valuable in terms of targeting appropriate psychological interventions within the context of a multidisciplinary approach to managing sickle cell pain. This has implications for health care costs.

References


A Study of the Geographic Distribution and associated Risk factors of Leg Ulcers within an International Cohort of Sickle Cell Disease Patients: The CASIRE Group Analysis

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Introduction
Vasculopathy is one of the hallmarks of sickle cell disease resulting chronic end organ damage. Leg ulcers is one of its sequelae occurring in ~5-10% in adult sickle cell patients with predominance in the Severe SS Genotype (Minniti et al 2010) and the CAR Haplotype. The sites that are most commonly involved includes medial and lateral aspects of the ankles. While leg ulcers have predominantly been studied in single center cohort studies, there are limited studies on the geographic distribution of legs ulcers and associated risk factor worldwide.

Aims & Objectives:
To determine the Geographic Distribution and associated clinical and demographic risk factors associated with Leg Ulcers in an international cohort of SCD patients.

Methods
The CASIRE group is an international multi-institutional collaborative group evaluating the clinical severity of adults and children with SCD through a validated questionnaire and medical chart review. Sites included academic centers in Italy, U.S., and Ghana. Patients were enrolled following formal consent/assent. The study was approved at each participating site’s institutional review board. We administered a comprehensive SCD medical history questionnaire to the participating subjects in U.S., Italy, and Ghana. We recorded subject’s demographic data including age, ethnicity, gender, and country of origin. Clinical data included history a leg ulcers, BMI, phenotype (SS, Sβ0, Sβ+, SC), Oxygen Saturation, hemoglobin level, leukocyte count, urine microalbumin and other SCD medical history including pain crisis patterns, acute chest syndrome (ACS), priapism, stroke, room air oxygen saturation, and avascular necrosis (AVN). We analyzed the frequency and associated clinical/demographic risk factors of leg ulcers using SPSS 22 statistical software.
**Results**

A total of 585 subjects were analyzed for this study with 261 subjects from U.S., 236 subjects from Ghana, 88 subjects from Italy. 57 (9.6%) of subjects reported a history of Leg ulcers. The majority leg ulcers occurred in adult (>18y/o) SCD patients (98.2%, p<0.001) within the Severe Genotype (96.5% vs. 3.5% in Mild Phenotype, p<0.001). Demographically, Leg Ulcers patients were more likely to be Male (62.7%, p=0.010) and from the Ghanaian Site (82.5% N=47 vs. 17.5% N=10 from US/Italy, p<0.001). Clinically, Patients with Leg Ulcers were more likely to be hypoxic (O2 Saturation Room Air: 95.5% vs. 97.4%, p=0.025) underweight (BMI <5th%tile: 33.3% vs. Non-Underweight 8.2%, p<0.001), more anemic (Hemoglobin 7.6 vs 9.3 g/dL, p<0.001), more hemolytic (TBili 3.6 vs. 2.4, p=0.036, AST 54 vs. 42 p=0.035) with more leukocytosis (12.9 vs. 10.4 1000/ul), more thrombocytosis (438 vs. 367 1000/ul, p=0.004). Although there was no significant association with microalbuminuria in Leg Ulcer patients (p=0.106), the reported higher Creatinine (0.79 vs. 0.52, p=0.003) and more urine acidosis (Urine ph= 5.7 vs. 6.0, p=0.002) suggests some associated related renal dysfunction. Within the Leg Ulcer Group, 35% of patients experienced Leg Ulcers for past 7 years, 59% reported recurrent leg ulcers. There was no significant relationship between leg ulcers and age, stroke, pain crises patterns, or priapism.

**Conclusion**

This is of one the 1st comprehensive analysis of Leg Ulcers prevalence and SCD demographic and clinical risk factors within a Cohort in International Sickle Cell Disease Patients. Multiple factors possibly contribute to the development of Leg ulcers. West African Background, Male Gender and being an Adult are associated demographic risk factors for Leg Ulcers in our Cohort. Associated leukocytosis and thrombocytosis suggests increased adhesion within the vessel bed as a contributing factor to leg ulcer development. Further, severe anemia, lower oxygen saturation, and hemolysis (elevated Bili, AST) supports the preceding prevailing findings of associated hyperhemolytic phenotype with this group. Renal Acidosis and higher creatinine levels supports possible renal dysfunction despite its lack of association with microalbuminuria. Further studies are needed in a larger cohort to validate these findings.
Venous Thromboembolism in Sickle Cell Disease

Professor Kathryn Hassell

Sickle cell disease (SCD) is a biologically active disorder characterized by intermittent hypoxia, inflammation, vascular activation/injury/remodeling and for which medical interventions are frequently required, including hospitalizations, surgery, and indwelling vascular devices. As for other severe systemic disorders, SCD is associated with markers of coagulation activation and endothelial changes that may lead to an increased risk of venous thromboembolism (VTE). Surprisingly scant literature is available to understand the overall risk of VTE in SCD, but there are some data to suggest that individuals with SCD may be at an increased risk of VTE during hospitalization, pregnancy, and with placement of indwelling catheters.

Current published guidelines regarding prevention of VTE do not explicitly address individuals with sickle cell disease. Most SCD patients, especially those with HbSS/Sβthalassemia, should be considered for VTE prophylaxis when hospitalized based on the medical severity of the illness. Prophylaxis after major surgery, including orthopedic surgery, may be quite reasonable, although this has not been carefully studied. However, as is true in other populations at risk for VTE, it is not clear if VTE prophylaxis should be routinely provided in the setting of pregnancy or with the use of indwelling catheters in the absence of a history of VTE. Remarkably, there are no data regarding the risk of VTE with estrogen-containing conception use in SCD.

Current guidelines regarding treatment of VTE similarly do not address those with SCD. Clinical experience suggests that standardapproaches to treatment appear to be successful. However, caution is warranted when using agents that are cleared renally, including low-molecular-weight heparins and the oral Xa- and IIa- inhibitors, as the level of renal insufficiency may be under-represented by creatinine. The lack of recognition of CKD may potentially lead to drug accumulation which would not be detected in the absence of monitoring. Duration of anticoagulation may be guided by the same principles as for other populations with VTE, considering aspects including the higher risk of recurrence after an unprovoked event as compared to that associated with a transient risk factor such as contraception, surgery or a catheter which has subsequently been removed. The impact of ongoing underlying prothrombotic changes in SCD has not been evaluated in these contexts.

While SCD likely represents a “hypercoagulable state”, the clinical severity of this phenotype is not yet well-characterized or studied. Until further studies are conducted, comparisons with other hypercoagulable states such as carriers of Factor V Leiden and/or other systemic illness such as lupus erythematosus may inform clinical decision-making about the prevention and treatment of VTE in sickle cell disease.


Dr. Hassell is a Professor of Medicine in the Hematology Division at the University of Colorado Denver, directs the Colorado Sickle Cell Treatment and Research Center and supervises the Hemoglobinopathies Newborn Screening Follow-Up program for the states of Colorado and Wyoming. She has an academic clinical practice at the University of Colorado where 150 adults living with sickle cell disease are managed and offers a large thrombosis consultative service, also supervising a pharmacy-directed warfarin monitoring clinic with over 600 patients. For more than 20 years, Dr. Hassell has been actively involved in the design, conduct and monitoring of clinical research studies in hemoglobinopathies, with an emphasis on adult sickle cell disease, and in venous thrombosis, with an emphasis on new anticoagulants. She has served on and chaired international steering committees for multi-center trials as well as data/safety monitoring boards. Dr. Hassell has participated in multiple national projects sponsored by the NIH, HRSA, and CDC related to clinical research, health services, and disease management guideline development.
Pulmonary Hypertension in Sickle cell disease

Associate Professor Elizabeth Klings

Pulmonary hypertension (PH) occurs in 6-11% of HbSS adults and is defined as a mean pulmonary arterial pressure \( \geq 25 \text{ mmHg} \) by right heart catheterization. Hemodynamically, these patients can have features of pulmonary arterial (or pre-capillary) hypertension, pulmonary venous (or post-capillary) hypertension or both, all of which are associated with reduced survival. Recently, the American Thoracic Society sponsored clinical guidelines for the diagnosis and treatment of PH in sickle cell disease to try to clarify the diagnostic and treatment strategies of this condition for clinicians. Objectives for this session include understanding: 1) the epidemiology and pathogenesis of PH in sickle cell disease; and 2) diagnosis and treatment of PH in sickle cell disease. There will be a discussion of unanswered questions in PH of sickle cell disease and future research needs in this field.
MEET THE EXPERT

Hydroxyurea therapy in sickle cell disease

Professor Kathryn Hassell

This “Meet the Expert” session will review current clinical considerations in the use of hydroxyurea in the management of sickle cell disease (SCD).

Although the efficacy of this drug is mediated primarily through increased fetal hemoglobin (HbF), the genetic influences on HbF levels in sickle cell disease are still being elucidated, and our understanding of the pharmacogenomics of hydroxyurea is extremely limited (1). Furthermore, relatively little is known about the pharmacokinetics of hydroxyurea, although the bioequivalence of the liquid and capsule formulations has recently been reported (2).

We will summarize the history of clinical trials leading to the current rationale for hydroxyurea therapy in SCD, including its beneficial effects on mortality, but we will focus on recent information from trials that include evaluation of its effects on organ function (3). Benefits in brain, splenic, renal, pulmonary, and retinal function have been reported, but the effects of hydroxyurea on organ function have been less robust than those seen in the reduction of acute vasoocclusive events (4-6).

The recommendations regarding hydroxyurea from the 2014 NIH Evidence-Based Management of Sickle Cell Disease Expert Panel Report will be reviewed briefly (7). Concerns regarding the drug's long-term safety and toxicity have focused on spermatogenesis, but data are still limited (8). Another controversial area is what the appropriate target dose should be: escalation to maximum tolerated dose (MTD) or maintenance at a fixed dose of 20 mg/kg/d (or perhaps even at a lower dose of ~10-15 mg/kg/d). Studies to address this question are currently being generated.


The role of prevention programs in thalassemia

Associate Professor Antonis Kattamis

It is estimated that around 7% of the world’s population carry a haemoglobinopathy gene, and about 500,000 patients are annually born with a haemoglobinopathy disease, of whom 300,000 with thalassemia. The majority (around 90%) of heterozygotes affect populations of Africa, Middle East and Asia. β-thalassemia trait is found in high frequencies in Mediterranean and Middle Eastern populations, while in Asia both α- and β-thalassemia trait is observed.

The health burden posed by thalassemia is directly related to the prevalence of thalassemia trait in the population. Current therapy with regular transfusions and systematic treatment of iron overload has modified thalassemia from a fatal disease of childhood to a chronic disease of adulthood with a reasonably good quality of life and continuously increasing life expectancy. Nevertheless, the cost for this chronic treatment is high and is estimated in the several dozen thousands € per patient per year. Thus, providing appropriate health services to an uncontrollable increasing number of patients is not sustainable, even for advanced health care systems. In this context, during the last decades, national programs for the prevention of thalassemia were implemented in many countries, resulting in a considerable change of the epidemiology and of health burden of thalassemia. The structure of the prevention program needs to be adapted to each country, taking into account the specific genetic background and the needs of the population, the available resources and mainly the local beliefs and customs. The thalassemia prevention program in Greece has been very successful and has allowed the decrease of new cases of thalassemia from around 250 patients/year to <10 patients/ year. Recent data showed that for further decreasing the number of new cases in Greece, selected groups of the population need to be targeted.
Renal Complications of sickle cell disease

Dr Claire Sharpe

As the life expectancy of patients with sickle cell disease (SCD) continues to improve, the spectrum of complications suffered by these patients has shifted towards chronic disease. Sickle cell nephropathy (SCN) is a well-known complication of the condition which is now recognised to be a much more prevalent problem, particularly in older patients. Early epidemiological studies characterized patients with end-stage renal failure and HBSS disease to be in their early twenties with a life expectancy of less than 30 whereas more recent observational data has suggested that it is becoming increasingly prevalent and a major cause of death in patients over the age of 60. It is therefore important to recognise the early signs of SCN, and other factors which may influence the course of chronic kidney disease, so that we may identify patients who are at risk of developing renal failure and intervene early.

The relatively hypoxic and hyperosmolar environment of the kidney inner medulla promotes polymerization of deoxygenated haemoglobin S and subsequent sickling of erythrocytes, resulting in impaired renal medullary blood flow, microinfarcts and papillary necrosis. Alongside this the persistent anaemia and high cardiac output, lead to glomerular hypertrophy and hyperfiltration. Over time the fine network of blood vessels in the kidney medulla is destroyed and the swollen glomeruli become scared and renal impairment sets in. Clinically, the early stages of SCN are associated with polyuria and low serum creatinine followed by microalbuminuria, proteinuria and in 10-15% cases end-stage renal failure.

This talk will cover the pathophysiology of sickle cell nephropathy, how to diagnose and monitor renal complications, what treatment options are available to prevent progression and how best to manage patients with end-stage renal failure with dialysis and transplantation. It will be illustrated with examples from our own patient population.
Impact of a dedicated infusion clinic for acute management for adults with sickle cell pain crisis

Professor Sophie Lanzkron

Most adults with sickle cell disease (SCD) receive care for their acute painful episodes in an emergency department (ED) setting. In that setting patients with SCD wait longer for their first dose of parenteral pain medication than other populations of patients and both providers and patients are frustrated with the quality of care. Busy, urban ED’s might not be the ideal place for patients with SCD to receive care for a vaso-occlusive crisis, especially as there is a lack of a strong evidence base to guide management. Dedicated urgent care clinics have been shown to improve outcomes in SCD, but there has not been widespread adoption of this model of care. This talk will describe the impact of opening a dedicated treatment center for adults with SCD (SCIC) on patient outcomes and on hospital discharges.

Over the time period studied there were 3874 visits to the SCIC by 361 unique patients. 85% of those visits resulted in the patient being sent home. During the same time period there 3408 visits to the ED by 558 unique patients with SCD. The overall admission rate from the ED for these patients was 35.9% but decreased significantly over the time period falling to a rate of 20%. There was a significant decrease in readmissions over time for the entire Baltimore Metro area with the likelihood of readmission decreasing by 7% over time. The SCIC model provides adults with SCD access to high quality care that decreases the need for hospital admission and readmission suggesting that now is the time to expand on this model of care.
Pregnancy in Haemoglobinopathies

Dr Eugene Oteng-Ntim

Sickle cell disease (SCD) is the most common inherited disease worldwide and is associated with significant anaemia and severe intermittent pain. Pregnant women with SCD have increased morbidity and mortality so much so that in 1971 there was a recommendation against pregnancy. Clearly this is not the case currently but is the pregnancies still afflicted with adverse outcome? My presentation will describe findings from a recent national study of maternal and fetal outcomes comparing haemoglobin SS with HbSC. I will also summarise studies from different countries alluding to adverse pregnancy outcomes in relation to sickle cell disease both from high and low/middle income countries. With these adverse outcomes, should there be sustainable goal on sickle cell disease in pregnancy? I will address the obstetric management of sickle cell disease in pregnancy and where possible highlight areas where research may be needed.
Managing the cardiovascular complications in thalassaemia major

J. Malcolm Walker MD, FRCP.
Consultant Cardiologist UCLH, London
Founder & Clinical Director Hatter Cardiovascular Institute, UCLH, London

Although there has been a dramatic reduction in mortality in thalassaemia major (TM) in the last decade, cardiovascular complications of thalassaemia remain a frequent cause of morbidity and mortality.

The availability of methods to assess tissue iron burden, non-invasively using cardiac magnetic resonance scanning (cMRI) to measure the T2* parameter, has driven the improved management of these patients. However, access to this technology remains limited in those parts of the world which face the greatest challenge from thalassaemia and is rationed even in wealthy economies such as in the UK. Newer cMRI sequences may provide some improvements in the future, with decreased scanning times and improved sensitivity.

Echocardiography is easily accessible and has the capacity to provide repeatable, safe, cost effective and rapid assessments of the heart in thalassaemia. Echocardiography is widely available and our experience has revealed that it remains a valuable clinical tool in patient management, complementing cMRI and allowing the possibility of better managing the scarcer resource of cMRI imaging. It has previously been demonstrated that the global assessment of ventricular function using the ejection fraction (EF) can be misleading in some patients, remaining normal despite low values of T2*, denoting heavy myocardial iron overload and the risk of rapid cardiac decompensation. We have investigated newer, less load dependent and less image dependent parameters of ventricular function to assess patients with thalassaemia.

Future challenges will include the increasing incidence of arrhythmia, specifically atrial fibrillation (AF) in this ageing group of patients as they now can expect to survive the early, at risk, years of their condition. The risk of stroke needs to be precisely determined in this population and the thresholds for intervention with anti-coagulation need to take into account a likely increased thrombotic drive.

The multidisciplinary approach to management has proven successful in thalassaemia particularly in the treatment of cardiac complications, but the surviving cohorts now present with new clinical challenges, which we must be ready to address to prevent late tragic consequences, such as stroke.
Evaluation of Endocrine functions in Hb Eβ Thalassemia patients with special reference to assessment of growth and puberty

Dipanjan Haldar¹, Prantar Chakrabarti², R Bhattacharjee³, P Mukhopadhyay³, S Chowdhury⁴

Background
In India, more than 10,000 new cases of thalassemia are born every year. In Bengal, Eβ thalassemia accounts for more than 50% of the disease burden. To the best of our knowledge, no published data is yet available on growth, puberty and endocrine complications in these patients.

Aims & Objectives
The aim of this study was to determine the prevalence of growth failure, delayed puberty and pattern of endocrine dysfunctions in patients of Eβ thalassemia. The objectives were to study the correlation between type of endocrine dysfunction with various clinical parameters and serum ferritin levels.

Methods
All demographic details were recorded. Clinical examination, anthropometric measurements and assessment of puberty were done. Routine biochemical investigations and specific endocrinological tests were performed. Patients were put on specific endocrinological treatment and monthly follow up was done.

Results /Conclusions
69 patients with Eβ Thalassemia were prospectively evaluated. The mean age was 15.6 years. There were 42 males and 27 females (M: F ratio =1.6:1). All patients received oral iron chelation with deferasirox. 23 (33%) of patients had onset of symptoms prior to three years of age while 42 (61%) of patients received their first transfusion before fifth birthday. 52 (75%) patients required regular (>4 units/year) transfusions. 27(39%) of the patients were splenectomised.

29 (42%) of patients were found to have growth retardation. Primary hypothyroidism was present in 9.5% male and 11% female patients. None of the patients were diabetic.

20/42 (48%) male patients had delayed puberty. They had significantly earlier onset of symptoms (p =0.04) and were more frequently growth retarded (p=0.01) in comparison to patients with normal puberty. 35% of male patients with delayed puberty achieved puberty with no or short duration (6 months) of testosterone replacement.

11/27 (41%) female patients had delayed puberty. They had significantly (p=0.02) earlier age at onset of symptoms. 36% of female patients with delayed puberty spontaneously achieved menarche without hormonal supplementation. Serum ferritin was not significantly different in patients with delayed puberty (in comparison to patients with normal puberty).

In this study, different clinical predictors of severity and serum ferritin levels were analysed to study their association with delayed puberty in Eβ thalassemia patients. Similar studies conducted from different centers will help to confirm or negate our findings.

References-
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³ Associate Professor, Department of Endocrinology, IPGMER, Kolkata
⁴ Professor & Head, Department of Endocrinology, IPGMER, Kolkata

Transfusion therapy for thalassaemia – The ultimate goal

Dr Sara Trompeter

Whilst patients with thalassaemia have undergone life-saving regular transfusion regimens with much success over the last decades, there has been little change in knowledge or provision of blood for these patients until recently. In this session we will discuss the important advances that have been made to facilitate, understand, and improve transfusion practice for patients with thalassaemia.
PLENARY SESSION

The relationship between genotype, alloantibodies and splenectomy on transfusion requirements in Beta Thalassaemia major

Jonah Fox

Background
Studies of Beta Thalassaemia use a number of markers of severity including pulmonary, cardiac and endocrine function. Quantitative measures of transfusion requirements are rarely used, and even less so in Beta Thalassaemia major.

Aims & Objectives
This study aimed to measure the association between clinical parameters (genotype, splenectomy status and alloantibody status) and transfusion requirements in patients with Beta Thalassaemia major in an English Thalassaemia centre.

Methods
Clinical records for all 123 patients with Beta Thalassaemia major known to the transfusion unit at the Whittington Hospital in North London were reviewed. Thirty patients were excluded as they had insufficient data available to calculate their transfusion requirements in mls/kg/year. To calculate their requirements, patients had to have at least 6 months consecutive documentation of transfusion input, as well as an accurate weight recorded. For those with the required data, further data regarding the Thalassaemia genotype and the splenectomy and alloimmunisation status were sought. Relationships between these parameters and the yearly transfusion requirements were assessed.

Results were analysed using T-tests comparing the transfusion requirements of patients with a certain parameter that parameter against those without it. A normal distribution was not assumed.

With regards to genotype, patients with a specific Thalassaemia mutation that appeared more than 5 times in its homozygous or heterozygous form were studied with 2-tailed t-test performed against all other values for patients in whom genotype data was available.

With regards to alloantibody status, one tailed t-testing was performed comparing those with antibodies to those without. The same was done comparing those with two or more to those with only one, and comparing those with three or more to those with only two. For specific alloantibodies occurring five or more times, comparison was made with the rest of the alloimmunised population.

One tailed t-testing was performed comparing splenectomised to non splenectomised patients

Results/Conclusions
The study found no significant difference in transfusion requirements with regards to any of the genotypes studied, or to the presence of any specific alloantibody compared to the alloimmunised population. As expected, higher numbers of alloantibody were significantly associated with higher transfusion requirements, as was lack of splenectomy (all p<0.01).

Matteocci A, (2014)
Bordbar MR, (2014)
Overview of Transplantation in Haemoglobinopathies

Professor Alexis Thompson

The sole currently available curative option for sickle cell disease and thalassemia is hematopoietic stem cell transplantation. In general the source of transplanted stem cells can be matched sibling bone marrow, matched unrelated donor marrow, or cord blood. The overall survival and disease-free survival, and the incidence of graft versus host disease, other transplant related morbidities and mortality differ among donor sources. Outcomes can also vary with the choice of preparative regimen. This presentation will provide a historical perspective of stem cell transplantation for haemoglobinopathies and will focus on outcomes with conventional stem cell sources and conditioning.
Outcomes of Gene Therapy for – Thalassaemia major and severe Sickle Cell Disease viatransplantation of autologous hematopoietic stem cells transduced ex vivo with a lentiviral AT87QGLOBIN Vector

Professor Marina Cavazzana¹, Jean-Antoine Ribeil*¹, Emmanuel Payen*², Felipe Suarez³, Yves Beuzard², Fabien Touzot¹, Resy Cavallesco⁴, François Lefrere⁴, Stany Chretien², Philippe Bourget¹, Fabrice Monpoux⁴, Corinne Pondarre⁷, Benédicte Neven¹, Manfred Schmidt⁸, Christof von Kalle⁵, Laura Sandler¹⁰, Sandeep Soni¹⁰, Olivier Hermine¹, Stéphane Blanche¹, M. de Montalmbert¹, Salima Haceaïn-Bey-Abina¹,¹¹, Philippe Leboulch²,⁴,¹²

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¹⁰bluebird bio, Inc., Cambridge, MA;
¹¹Groupe Hospitalier Universitaire Paris-Sud, Paris, France
¹²Mahidol University and Ramathibodi Hospital, Bangkok, Thailand

(*these authors contributed equally)

Background
In patients with haemoglobinopathies, hematopoietic stem cell (HSC) gene therapy has the potential to induce production of functional \( \beta \)-globin in the red blood cell lineage with the aim of reducing or eliminating the symptoms of disease. Results for 2 subjects with \( \beta^0/\beta^E \)-thalassemia major treated in clinical study HGB-205 that were previously presented (EHA 2014, ASH 2014) suggested that transplantation with autologous CD34+ cells transduced with a replication-defective, self-inactivating LentiGlobin BB305 lentiviral vector containing an engineered \( \beta^A\text{-T87Q} \)-globin gene resulted in near-normal levels of total hemoglobin (Hb) and early transfusion independence.

Aims
Herein we provide additional follow-up data on these two subjects, as well as early safety and efficacy data on the first subject with sickle cell disease (SCD) treated with LentiGlobin BB305 gene therapy in HGB-205.

Subjects and Methods
After obtaining informed consent, subjects with \( \beta \)-thalassemia major underwent HSC collection via peripheral blood apheresis, while subject with severe sickle cell disease underwent HSC collection via bone marrow harvest. CD34+ cells were selected and transduced with LentiGlobin BB305 lentiviral vector. Estimation of the mean ex-vivo vector copy number (VCN) was obtained by quantitative PCR performed on pooled colony-forming progenitors. Subjects underwent myeloablation with intravenous busulfan, followed by infusion of transduced CD34+ cells. Subjects were monitored for overall safety including hematological engraftment, \( \beta^A\text{-T87Q} \)-globin expression (by high performance liquid chromatography) and transfusion requirements. Integration site analysis (ISA, by linear amplification-mediated PCR and high-throughput
sequencing on nucleated cells) and replication-competent lentivirus (RCL) assays were performed. Prophylactic pRBC transfusions were continued in sickle cell subjects who were transfusion dependent pre-treatment to maintain HbS <30%.

Results: As of February 2015, 2 subjects with β/β thalassemia major (Subjects 1201 and 1202) and 1 subject with βS β-severe sickle cell disease (Subject 1204, who was on prophylactic transfusion therapy for multiple veno-occlusive crises, acute chest syndrome and a silent cerebral infarct) have undergone treatment. The outcome of these subjects to date is shown in Table 1. No subject has experienced a drug product related adverse event, and ISA analyses demonstrate highly polyclonal reconstitution without clonal dominance. Both β-thalassemia major subjects remain transfusion-free for 14 and 11 months respectively, post-treatment. At their most recent visit (Month 4.5 post-treatment), Subject 1204 has a total hemoglobin of 12.0 g/dl, of which 24% is HbA\textsubscript{T87Q} (from 9.6% at Month 3) and 33% is HbS (from 14.7% at Month 3), with increasing levels of transduced cells (VCN) detected in peripheral blood. This subject has not had a post-treatment hospitalization for a SCD-related event.

Conclusion: The subjects with β-thalassemia major remain transfusion-free for 14 and 11 months. The subject with SCD demonstrates increasing production of HbA\textsubscript{T87Q} over time. Gene therapy using autologous HSC transduced with LentiGlobin BB305 lentiviral vector ex vivo is a promising approach for the treatment of patients with both β-thalassemia major and severe SCD.

Table 1. Demographics and Transplantation Outcomes

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (years) and gender</th>
<th>Genotype</th>
<th>BB305 Drug Product</th>
<th>VCN\textsuperscript{a}</th>
<th>CD34\textsuperscript{+} cell dose (x10\textsuperscript{6} per kg)</th>
<th>Day of Neutrophil Engraftment</th>
<th>Drug Product-related Adverse Events</th>
<th>Day of last pRBC transfusion</th>
<th>Last Study Visit</th>
<th>Amount of HbA\textsubscript{T87Q} at last visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with β-thalassemia major</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1201</td>
<td>18 F</td>
<td>β0/βE</td>
<td>1.5</td>
<td>8.9</td>
<td>Day +13</td>
<td>None</td>
<td>Day +10</td>
<td>12M</td>
<td>7.7/11.0</td>
<td></td>
</tr>
<tr>
<td>1202</td>
<td>16 M</td>
<td>β0/βE</td>
<td>2.1</td>
<td>13.6</td>
<td>Day +15</td>
<td>None</td>
<td>Day +12</td>
<td>9M</td>
<td>9.4/13.2</td>
<td></td>
</tr>
<tr>
<td>Subject with severe sickle cell disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1204</td>
<td>13M</td>
<td>βS/βS</td>
<td>1.2 / 1.0</td>
<td>5.6</td>
<td>Day +37</td>
<td>None</td>
<td>Day +88</td>
<td>4.5M</td>
<td>2.9/4.0/12.0</td>
<td></td>
</tr>
</tbody>
</table>

As of February 2015

\textsuperscript{a}VCN, vector copy number; F=female; M= Male for gender, and months for day of last follow-up
Abstracts
Day 3
Friday 9 October 2015
Management of Acute Chest Syndrome in Sickle Cell Disease

Dr Jo Howard

Acute chest syndrome is an acute illness in patients with sickle cell disease (SCD) characterised by fever and/or respiratory symptoms accompanied by a new respiratory infiltrate on Chest X-Ray. The British Committee for Standards in Haematology have recently produced guidance on its management using its standard methodology of systematic evidence review and production of recommendations using the GRADE system to quotes levels and grades of evidence.

Key recommendations include

Patients with SCD can present with ACS or it may develop sometime under onset of severe pain, therefore vigilance should be maintained throughout hospital admission.

ACS can be a severe life threatening condition, early recognition of progression to respiratory failure is vital.

Essential investigations include chest X-ray, full blood count, basic biochemistry and blood group and screen. Blood cultures, sputum for microscopy and culture, and sputum and nasopharyngeal aspirate for viral testing should be performed if clinically indicated.

An infective cause is common and this should be considered in treatment algorithms.

All patients with ACS should be given prompt and adequate pain relief; incentive spirometry has proven benefit in preventing ACS in patients with chest or rib pain and should be considered in all patients with ACS.

Simple (top-up) transfusion should be considered early in the hypoxic patient but exchange transfusion is necessary if there are severe clinical features or evidence of progression despite initial simple transfusion.

Blood should be sickle negative and fully matched for Rh (C, D and E) and Kell Bronchodilators should be sued if there are clinical features suggestive of a history of asthma or evidence of acute bronchospasm.

Hydroxycarbamide should be recommended for prevention of recurrent ACS, consider chronic transfusion for prevention of recurrent ACS if hydroxycarbamide is not effective.

Development of a New Adult Sickle Cell Disease Center within an Academic Cancer Center: Impact on Hospital Utilization Patterns and Care Quality

Biree Andemariam, MD and Sasia Jones, MPH
New England Sickle Cell Institute, University of Connecticut Health Center, Farmington, CT, USA.

Introduction
A national shortage of specialized centers with expertise in the management of adults with sickle cell disease (SCD) remains a concerning public health disparity. Yet, there is an abundance of cancer centers whose operational infrastructure is not only suited to the treatment of the oncology patient, but also can provide medical and procedural care essential to the management of sickle cell disease. Our adult SCD center was formally established within an academic hospital-based cancer center in 2009. An evaluation of the impact of this new center was performed.

Methods
A retrospective chart review was conducted of all SCD encounters occurring five years pre- and post- SCD center establishment. Demographic, clinical as well as hospital utilization and care quality data were compared.

Results
The SCD population grew 650% from 22 to 165 patients. Following establishment of the SCD center, patients experienced greater average annual outpatient preventative visits for chronic disease management (1 vs. 4.1) and fewer average hospitalizations yearly (2.4 vs. 1). There was a decrease in hospitalization rates for management of acute pain (50% vs. 23%), average hospitalization length of stay (12 vs. 6 days), and the proportion of hospital discharges resulting in readmission within thirty days (60% vs. 40%). Hydroxyurea use among eligible patients increased from 30% to 90%.

Conclusion
Findings suggest that embedding adult SCD centers within existing cancer centers can positively impact patterns of health care utilization and improve the quality of care.

This abstract has been recently accepted for publication (in press, Journal of Racial and Ethnic Health Disparities).
Transition from Paediatric to Adult care…at work beyond the clinic visit

Mr Luhanga Musumadi

The demands of living with a chronic illness present additional challenges to normal adolescence development. Young people with sickle cell disease (SCD) are faced with dealing with recurrent painful episodes, multiple hospital admissions and attending regular out-patient clinics for disease monitoring. This may put a significant amount of strain on them, particularly at a time when they are undertaking their GCSEs and entering higher education. The implications are far reaching and wide ranging, affecting not just their education, but also their social and employment opportunities, consequently may also threaten their quality of life (Thomas et al, 2009).

This highlights the need for developing age appropriate services that support young people with chronic illness to achieve their maximum potential in terms of education, health, development and well-being (DOH, 2008).

The “You’re welcome” quality criteria for young people friendly health services (DOH, 2011) advocates the need for more opportunities for joined up working between primary and secondary care, as well as local authorities and commissioners.

This presentation highlights the role of the multidisciplinary team working through a comprehensive care approach in addressing the needs of adolescents with complex care needs. Case studies are used to demonstrate examples of multidisciplinary team working.
Extended nursing role in patient care for haemoglobinopathies

Mr Neill Westerdale

The role of ANP in nursing has been developed to allow for an increase in their levels of responsibility, whilst at the same time allowing them to develop beyond that of a generalist nurse within the clinical practice setting. The ANP role for adult SCD patients was developed in 2008 in response to changes in the delivery of care for adult SCD patients at GSTT. This included changes to the admissions processes, which included the need to support patients across two sites (Guy’s Hospital and St Thomas’ Hospital). The ANP independently reviews SCD patients in SCD crisis and arranges admission and transfers cross site or discharge home if appropriate. The ANP also undertakes advanced physical assessments, complete referrals, and initiates investigations and review results. The ANP also triages SCD patients who want to access the nurse led pain service for patients in crisis in the haematology day unit on (GH) site. The ANP also works within the adult SCD clinic running an independent nurse led clinic for patients on hydroxycarbamide, including offering a bleed and go service that helps to reduce the treatment burden for patients. In clinic the ANP also undertakes annual reviews, which are comprehensive health assessments on adults SCD patients.
Introduction
It is well-known that sickle cell disease (SCD) leads to a state of hyper-metabolism and catabolism [1] leading to increased myocardial demand and a pro-inflammatory state [2]. Although malnutrition and SCD are both relatively common in parts of Ghana [3], the impact of comorbid malnutrition on the SCD phenotype has not been published in an international cohort of patients. Chawla et al published on the clinical phenotype of underweight pediatric SCD patients in a U.S. cohort and revealed male gender, older age, lower hemoglobin and SS phenotype was statistically associated with being underweight [4].

Aims & Objectives
The goal of this study was to determine in an international cohort of adult and pediatric patients with SCD the relationship between underweight (<5th percentile body mass index (BMI)) and clinical markers of SCD severity

Methods
The CASIRE group is an international multi-institutional collaborative group evaluating the clinical severity of adults and children with SCD through a validated questionnaire and medical chart review. Sites included academic centers in Italy, U.S., and Ghana. Patients were enrolled following formal consent/assent. The study was approved at each participating site's institutional review board. BMI categories (underweight, normal, overweight and obese) were calculated using the formula weight (kg) / [height (m)]². BMI alone was used to classify adults into weight categories. For children, the weight categories were determined using age-associated BMI percentile charts. Both demographic and clinical data were obtained. Demographic data included age, gender, and country of residence. Clinical data included height, weight, hemoglobin phenotype (SS, Sβ0, Sβ+, SC), hemoglobin level, leukocyte count, urine microalbumin and SCD medical history that included pain crisis frequency, emergency department (ED) utilization frequency, as well as history of leg ulcers, acute chest syndrome (ACS), priapism, stroke, room air oxygen saturation, and avascular necrosis (AVN). The relationship between BMI and both demographic and clinical data was analyzed using SPSS statistical software.
Results
There were 676 total patients in the study of whom 56% were under age 18. Patients were equally distributed between developed and developing countries (48% U.S./Italy vs. 52% Ghana). Sixteen percent of the patients were underweight (n=109). Compared to normal, overweight and obese patients, underweight SCD patients were overall more likely to be male (79% vs. 52%, p<0.001), Ghanaian (83% vs. 47%, p<0.001), report less frequent pain crises per year (<3/year 82.2% vs. 64.6%, p<0.001), have higher annual self-reported rates of ED utilization for pain (>3/year 34.8% vs. 21.6%, p=0.01), have no prior history of acute chest syndrome (35.5% vs. 18.7%, p=0.001), have a history of leg ulcers (11% vs 4.4%, p =0.005), higher leukocyte count (12.2 vs 10.5 x1000/ul, p=0.007), and lower hemoglobin (8.1 vs 9.2 g/dL, p<0.001). In the U.S./Italy cohort only, underweight BMI was associated with greater microalbuminuria (60.8 vs 25.2 mg/gm, p= 0.04). In the SS and Sβ0 thalassemia group only, underweight patients were more likely to have a history of AVN of hips (25% vs 13%, p=0.02) and humeral head (13.8% vs 4.3% p=0.03) compared to non-underweight patients. There was no significant relationship between underweight BMI and age, hemoglobin phenotype, height, stroke, priapism, or room air oxygen saturation.

Conclusion
We are the first to describe the clinical severity markers of an underweight SCD patient cohort that includes adults as well as individuals from both developed and developing nations. Moreover, we have identified that underweight SCD patients demonstrate a distinct clinical phenotype. Although less likely to experience pain crises and develop ACS, they are more likely to have far less clinically apparent complications such as AVN and early signs of kidney damage. The strikingly high prevalence of underweight BMI in the Ghanaian cohort is particularly noteworthy and also warrants further investigation.

References:
Global burden of Sickle Cell Anaemia

Dr Frédéric B. Piel
University of Oxford, Oxford, UK

Reliable estimates of population affected by diseases are necessary to guide efficient allocation of public health resources. Sickle haemoglobin (HbS) is the most common and clinically significant haemoglobin structural variant. Using a database of sickle haemoglobin surveys, we previously created a contemporary global map of HbS allele frequency distribution within a Bayesian geostatistical model. The pairing of this map with demographic data enabled calculation of global, regional, and national estimates of the annual number of AS and SS neonates. Accounting for local heterogeneities and demographic factors, we estimated that the global number of neonates affected by HbS in 2010 included 5,476,000 (IQR 5,291,000–5,679,000) AS newborns and 312,000 (294,000–330,000) SS newborns. Although these global estimates were higher than previous conservative estimates, we recently studied the magnitude of deviations from Hardy-Weinberg assumptions in newborn screening surveys of sickle cell disease and the impact of such deviations on newborn estimates. Our analyses suggest that the above estimates of SS annual births might represent underestimates of up to one third in sub-Saharan Africa and one half in the Middle East. In addition to methodological advances to refine these estimates, epidemiological studies are essential to assess changes and improvement in the prevention and management of sickle cell disease, particularly in low- and middle-income settings.
Lessons from 22 years in improving health of children and pregnant women with SCD in a Sub-Saharan Africa setting

Dr Mohamed Cherif Rahimy,

Professor of Pediatrics and medical Genetics, Faculty of Health Sciences, University of Abomey-Calavi, Director, National SCD Institute of Benin Republic, West Africa, dedicated to the care of affected Infants and Pregnant Women.

Many of the SCD-related health problems can be prevented or treated by readily available medical interventions. The major concern is that these advances are still limited to developed countries dealing with few patients, exemplifying the increasing health inequity, between developed and developing countries. The vast majority of children with SCD live in Sub-Saharan Africa where about 500,000 affected babies are born each year, and it is likely that more than 50% of those children die from the condition before the age of five, without ever having even been diagnosed. In developed countries continuous comprehensive care program (CCCP) from diagnosis at birth, prior to onset of symptoms, has been shown to decrease SCD-related morbidity and mortality. Given the cultural superstitions and poor socioeconomic background of sub-Saharan countries, such programs need substantial adaptation tailored to the local realities which otherwise will inevitably compromise compliance of parents and consequently enrollment of initially asymptomatic SCD children into a CCCP. For 22 years now, we have established a neonatal screening for SCD program sustained by a CCCP in Cotonou, the largest city of the Republic of Benin. The CCCP includes intensive socio-medical intervention programs tailored to local constraints to overcome drawbacks and to ameliorate the disease course. The strategy implemented by a trained and committed team was based on identification and active information and sensitization of the pregnant at-risk-women prior delivery, followed by a voluntary enrollment into the screening and follow-up programs. During the initial period, newborn testing was asked by 79.3% of the sensitized at-risk-women of whom 81% did ask for the result of the test and 85% of eligible SCD babies were effectively enrolled into the CCCP. Starting from the fourth year, more and more at-risk mothers aware of the existence of such programs brought their offspring for testing. The programs also permit enrollment of children diagnosed on the occasion of acute events and early diagnosis of SCD in many infants. Faced with the poorer outcome of pregnancy in SCD, a specific care program was implemented. Furthermore, by necessity, several additional programs have been designed and implemented such as a cost-effective outpatient management of fever, a frequent acute event in SCD children, and a non-invasive management of the hip avascular necrosis program. Initial analysis indicates a remarkable reduction of the morbidity and mortality burden and satisfactory physical growth. The under-five mortality rate is 15.5 per 1000 in our series of SCD children, which is amazingly 10 times lower than the overall under-five mortality rate in the Benin Republic; the observed maternal mortality rate is 1.8%. About 80% of enrolled children are still regularly followed. These results were important determinants in inciting our Ministry of Health to institute a National SCD Program and to convince the Government to create the National SCD Institute, dedicated to the care of affected Infants and Pregnant Women. Finally, we are forming a cohort constituted of more than 3,000 patients prospectively and homogenously followed from early infancy to document the history of SCD in our setting. Very striking, a specifically tailored strategy relevant to the Africa setting unique conditions can result in improved clinical presentations of SCD.
Addressing the Challenge of Sickle Cell Disease

Professor Kwaku Ohene-Frempong, MD

In recent decades, diseases not passed on from person to person, so-called non-communicable diseases (NCDs), have emerged as the leading public health issues, as communicable diseases fade with improvements in education, sanitation, water quality, nutrition, and immunization. Trapped between these two major groups of disease are genetic disorders. Passed on from person to person, but classified as NCD, genetic diseases are not necessarily improved by changes in income of countries.

Sickle cell disease, as old as it is in origin, is still emerging as a public health challenge. Whereas in the past its prevalence was kept low by communicable diseases, mostly infection, SCD continues to grow in significance as a major cause of death, disability, and illness in many countries, especially those of sub-Saharan Africa. Public health systems in low-income countries, shifting from communicable to NCDs, have not been prepared to deal with chronic genetic diseases. The challenges of SCD and their solutions, may serve as lessons in solving some of the difficult issues related to NCD.

Genetic diseases tend to be chronic and intergenerational. Their persistence and recurrence within families and ethnic groups easily become fodder for superstition, stigma, and neglect. The first challenge of SCD is the view that it is a disease of a particular people. From traditional, and modern scientific perspectives, SCD remains a social and medical stigma in many societies.

The second challenge is lack of education and training. Modern knowledge about SCD has been developed largely outside the areas of the world with the highest burden of the disease. The assumption, often erroneous, is that, like malaria, health workers in sub-Saharan Africa for example, must be expert at managing SCD. However, familiarity alone does not produce expertise. With low expectations from the affected population, health workers in the high prevalence areas are under little pressure to upgrade their knowledge of and practices in SCD.

A third area of challenge is the public health perception of SCD. While many health workers are aware of SCD in the high prevalent countries, the impact of the disease on public health is less apparent. If most fatalities from a disease are in young children and the causes of death are non-specific in symptomatology and mimic other more common diseases, accurate data may be lacking. That makes it difficult to convince public health officials of the importance that disease. Very few countries in sub-Saharan Africa have organized programs for SCD within their public health services.

Finally, there is the challenge of delivering proven services to people with SCD in low-income countries. Must patients in low-income countries be left out of gains made in high-income countries? Can paradigms of management of SCD be designed for low-income countries that parallel those in high-income countries in outcomes? This is a challenge that must be addressed in innovative and bold research.
PARALLEL SESSION H

Exploring Health-Related Quality of Life and health behaviours in Children with Sickle Cell Disease

Constantinou, C., Payne, N., van den Akker, O., & Inusa, B.

Background
Children with sickle cell disease (SCD) may experience psychological distress, social isolation and an impaired Health-Related Quality of Life (HRQL). Clinical manifestations such as pain and psychosocial factors may be managed, to a certain degree by engaging in daily health behaviours including a high protein diet, hydration and avoiding excessive exercise. However, children's ability to engage in healthy behaviours may be undermined by their condition, social influences, their environment and psychological factors. These behaviours have rarely been studied in paediatric SCD populations and have not been examined in relation to HRQL. Nor have these issues been studied in the siblings of children with SCD. Moreover, HRQL studies have failed to adopt the World Health Organization's (WHO) definition of HRQL as the discrepancy between individuals' perceived self and ideal self.

Aims & Objectives
To explore the HRQL and health behaviours (diet, fluid intake and physical activity levels) of children with SCD, including any differences between their current and ideal self, compared to that of their healthy siblings.

Methods
Thirty-two semi-structured interviews facilitated by children's drawings of their perceived and ideal selves were conducted with children with SCD and healthy siblings aged five to twelve years old.

Results
Preliminary thematic analysis of the transcripts and drawings revealed seven themes 1. Discrepancy in HRQL: Discrepancies in current and ideal selves were found. Children with SCD would like to participate in more physical activities and to have more family or friends whereas their healthy siblings have greater discrepancies in their psychological state and have more expectations/are more ambitious. 2. Relationships and/or Support: On the whole children with SCD and healthy siblings positively described family members and friends. However, many children do not have a relationship with their fathers and some children with SCD do not have friends and describe themselves as depressed, although healthy siblings did not experience these issues. Teachers are often encouraging and are confidantes. 3. Diet and Fluid: Children have a varied diet. At home children eat cultural food and do not regularly have ‘unhealthy food’ such as desserts whereas at school they eat British foods and mostly eat ‘unhealthy food’. The majority of healthy siblings only drink water at school whereas half of children with SCD drink water at home too. 4. Influences on health behaviours: Children discussed internal (i.e. self-awareness) and external influences (i.e. their parents, school and media influences) on health behaviours. Parents influenced children to eat healthily, however few encourage them to drink water. Children with SCD were not encouraged to participate in physical activities whereas their healthy siblings are. 5. Impact of SCD: SCD has an impact on children's emotional state as well as practical implications including affecting their education and social lives. Healthy siblings sought comfort in their religious beliefs whereas children with SCD did not discuss religion. 6. Secrecy: Most children are aware that they or their sibling have SCD and have a reasonable knowledge about the condition. It is common for children with SCD and their parents to be secretive about their condition and a couple of children with SCD experienced stigma. 7. Coping with Pain: Children with SCD have different coping strategies for dealing with their pain, for example, diet, fluid intake, reducing their physical activity and taking medication or hospital treatment. Conclusions: There is a greater discrepancy between the perceived and ideal selves of healthy siblings compared to children with SCD in some areas of HRQL which is unexpected but may be due to children with SCD having lower expectations of their ideal self compared to their healthy siblings.
Prevention and Management of Stroke in Sickle Cell Disease in Nigeria; Progress of the SPIN Trial

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Department of Haematology and Blood Transfusion, Bayero University/Aminu Kano Teaching Hospital, Kano, Nigeria.

Nigeria has the highest number of children with sickle cell disease (SCD). Stroke is one of the most devastating complications in these children with SCD. In high income countries regular blood transfusion therapy for patients with elevated transcranial Doppler ultrasound (TCD) measurements is associated with an at least a 90% relative risk reduction in overt strokes when compared to no treatment. However, monthly blood transfusion therapy is not an option in Africa due to its high cost, unavailability of blood and unsafe transfusion practices. Therefore, we decided to conduct a phase III trial to determine the efficacy of hydroxyurea as a suitable alternative to blood transfusion for primary prevention of stroke in children with SCD in Sub-Saharan Africa. In preparation for this Phase III trial, we conducted a feasibility trial NCT01801423; (1R21NS080639-NCE) and achieved the following milestones: 1) demonstrated the feasibility of the first NIH-funded SCA stroke clinical trial in Africa, with 92% of the eligible participants enrolled. 2) Showed favorable data that moderate dose hydroxyurea (HU) (~20mg/kg/day) is safe. 3) Demonstrated that HU therapy may be effective for primary stroke prevention (3 months after starting HU therapy, 2/3rd of the SPIN Trial (n=25) children had baseline elevated TCD levels decreased to normal. 4) Revealed very good adherence to HU therapy based on biological correlates (mean corpuscular volume) and the validated Morisky Medication Adherence Scale.

Based on these results of the feasibility trial, we are now poised to conduct the definitive trial, our primary hypothesis for this phase III trial is that moderate dose HU therapy results in a 66% relative risk reduction (9 to 3 events per 100 patient years), when compared to low dose HU therapy for primary prevention of strokes.

After completion of the first ever NIH sponsored stroke phase III SCD trial in Africa, we will be in a unique position to determine whether moderate dose HU therapy can prevent thousands of strokes, the results of which will not only benefit children and families with SCD in Sub-Saharan Africa but will provide an alternative to blood transfusion for primary prevention of stroke in high income countries.
Neurocognition in sickle cell disease

Professor Fenella Kirkham, Michelle Downes and Jamie Kawadler
UCL Institute of Child Health, London, UK

Sickle cell disease (SCD) is the most common cause of childhood stroke world-wide. Magnetic resonance imaging (MRI) is routinely used to detect additional silent cerebral infarction (SCI), as intelligence quotient (IQ) is lower in SCI as well as stroke. In a systematic review and meta-analysis of 19 articles with a SCD paediatric population, MRI information and Wechsler IQ, mean differences in IQ between 3 groups: Stroke vs. SCI, SCI vs. no SCI, and no SCI vs. healthy controls, were significant. Stroke patients had lower IQ than SCI patients by 10 points (6 studies), SCI patients had lower IQ than no SCI patients by 6 points (17 studies), and no SCI patients had lower IQ than healthy controls by 7 points (7 studies).

Neuropsychological functioning may decline with age in comparison to peers without SCD, even with no clinical history or MRI evidence of stroke. Neurocognitive deficits appear early in development, are detectable in the first three years and impact school readiness. It may be difficult to improve IQ by the time it is obviously a problem in later childhood. Therapeutic strategies might therefore focus on predicting and preventing cognitive difficulties in young children and in appropriate medical treatment to improve potentially reversible specific difficulties, e.g. with attention, memory and processing speed, which underpin cognitive success.

The frontal lobes have a protracted period of development in comparison to other brain regions and are the regions most susceptible to pathology in SCD. They are also known to play a prominent role in the brain network underlying executive function. Low oxyhaemoglobin saturation (SpO\textsubscript{2}) is a pathological process common to both SCD and sleep-disordered breathing (SDB), which has prevalence rates as high as 41\% in SCD. Processing speed and executive deficits are detectable in London children with SCD, including preschoolers. There appears to be a specific link with low haemoglobin oxygen saturation (SpO\textsubscript{2}), for example in tasks involving processing speed, attention and executive control. Infants with SCD with lower SpO\textsubscript{2} make more errors on the object retrieval test of executive function. Older children with SCD show differences in grey and white matter structure, partly explained by lower SpO\textsubscript{2}.

In a cohort of young children attending the East London Sickle Cell clinic, 27\% of children aged 1 to 4 years with SCD had SDB. In our on-going study at UCL Institute of Child Health, 21 of 23 children with SCD between three and five were reported to snore by parents. In preschool children with SCD we found that those also diagnosed with SDB had lower scores on two measures of processing speed: NIH toolbox processing speed (p=.05) and WPPSI coding scores (p=0.01). Higher rates of parent-reported sleep problems were associated with poorer executive functioning on the Behaviour Rating Inventory of Executive Functioning-Preschool (p<.01).

Children with SCD and no apparent MRI abnormality have significantly lower IQ than healthy controls. In this chronic condition, other biological, socioeconomic and environmental factors must play a significant role in cognition. Hydroxyurea appears to improve cognitive function in young children, although there are few data. Early intervention for children with SDB and SCD, could also lead to improve processing speed and executive functioning.
The Significance of Silent Cerebral Infarcts in Children with Sickle Cell Anemia

Professor Winifred Wang

Silent cerebral infarcts (SCI) have been reported in up to 40% of children with sickle cell anemia (SCA). The significance of these lesions is incompletely understood and appropriate screening for and management of SCI have not been established. The SIT Trial led by Michael DeBaun demonstrated that SCA patients with SCI (but not abnormal TCD velocities), who were randomized at a mean age of 10 years to receive chronic transfusion, had significantly fewer episodes of new infarct (both overt stroke and SCI) over three years of follow-up when compared with non-transfused controls (1). However this difference was really due to the prevention of overt stroke (1 vs. 7 events) rather than prevention of SCI (5 vs. 7 events). The concluding recommendation of the SIT Trial was that a surveillance MRI of the brain in children with SCA should be performed when they are beginning elementary school.

Recently a cohort of 37 SCA patients at St. Jude Children’s Research Hospital who had had MRI/MRA of the brain performed at a very young age were analyzed after an average follow-up of 14 years (2,3). Their initial MRI/MRA exams had been performed between ages 7 and 48 months. In the retrospective analysis, 10 patients (27%) younger than age 5 years had been found to have SCI (Group I), as did 12 (32%) older than 5 years (Group II). Fifteen (41%) had no lesions (Group III). Overt stroke or TIA occurred in 5/9 (56%) in Group I. Most Group I patients had progressive MRI abnormalities, concurrent stenosis, decreased cognitive ability, attention/executive function deficits and hindered academic attainment. A significantly greater proportion of subjects in Group I had subsequent neurological events (p<0.006), progressive ischemia (p<0.001) and vascular stenosis (p<0.006) than in Groups II and III. SCI in young children with SCA also appeared to predict poor cognitive function and academic performance. We concluded that children < 5 years of age may benefit from MRI/MRA evaluation and should be considered for aggressive intervention when SCI are detected.

The findings from the SIT Trial and the St. Jude cohort raise several important questions: (1) Should “screening” MRI/MRA exams be routinely performed in preschool/early school age children? (2) What are the logistical and medical cost implications of carrying this out? (3) What are the “proven” detrimental effects of SCI? Do they warrant prophylactic intervention? (4) If intervention is warranted, what is the optimal choice? These questions will be addressed in the talk, but satisfactory answers are not guaranteed.

Burden of adult sickle cell disease: management and challenges

Dr Eugenia Vicky Asare

Introduction
In Africa, sickle cell disease (SCD) is a major public health problem with over 200,000 babies born per year. Ghana has a large burden of SCD with approximately 15,000 (2%) of Ghanaian newborns per year having the disease; 55% of whom have sickle cell anaemia (SCA). SCD is associated with significant childhood and adult morbidity and mortality in Ghana. With improvements in medical care however, most babies will reach adulthood; with a subsequent increase in the prevalence of chronic complications. The Ghana Institute of Clinical Genetics (GICG) was established in Korle- Bu, Accra, Ghana, in 1974; and currently provides comprehensive out-patient care to adults with SCD.

Methods
A retrospective review of all SCD patients aged ≥ 13 years, who presented to GICG from January, 2013 to December, 2014. The number of registered patients, attendance, phenotypes, demographics, pattern of attendance and common complications were extracted.

Results
Currently, the GICG has over 25,000 patients registered with the following phenotypes; HbSS: 11,984, HbSC: 10,218, others: 3,189.

In 2013 and 2014, total attendance was 10,597 with 251 new patients and 10,181 with 182 new patients respectively. Attendance according to phenotypes yearly were, HbSS (approximately 60% of patients): 6494 (2013) and 6147 (2014); HbSC (approximately 35%) of patients): 3581 (2013) and 3549 (2014); other sickle cell syndromes (approximately 5% of patients): 513 (2013) and 470 (2014). The youngest patient was 13 years old, and the oldest 89 years old. Out of the total attendance, outpatient clients for 2013 and 2014 was 8266 (78%) and 7526 (74%) respectively; and those detained for urgent care was 2331 (22%) and 2655 (26%); for which 51 patients were admitted on the teaching hospital ward. In 2014, 91 (19.2%) clients were referred to Obstetrics and Gynaecology; 75 (15.9%) to Orthopaedic surgery, out of which 53 (70.7%) of them had avascular necrosis; and 73 (15.4%) to Ophthalmology clinic; 61 patients with chronic leg ulcers were seen at the clinic.

Conclusion
Even though the clinic sees a large volume of patients, it is able to cater for them amidst challenges. These include absence of a well-built infrastructure; proper channels for patient education and counselling, early diagnosis, and follow-up. Most of the patients also have financial constraints and are unable to assess basic healthcare and basic health maintenance requirements.

Our achievements include a Nephrology clinic which runs alternate weekly, and soon to start Ophthalmology clinic. We have approximately 1000 patients aged >40 years old. We are also involved with community education; and research.
Perspectives in Genetics and Secondary Prevention in Sickle Cell Disease

Professor Ambroise Wonkam
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Management of sickle cell disease (SCD) in Africa needs to be accompanied by various preventive strategies, including early detection via prenatal genetic diagnosis (PND). Contrary to Cameroonian doctors who considered termination of an affected pregnancy (TAP) for SCD in 36.1%, the majority of parents (62.5%) with affected children accepted TAP in principle. In practice, most women opted for TAP (90%), justified by a huge psycho-social burden. The ethical and legal challenges of PND prompted the need to explore the use of genetics for secondary prevention of SCD. In 610 Cameroonian SCD patients, the genomic variations in two principal foetal haemoglobin-promoting loci were significantly associated with foetal haemoglobin levels. In addition, the co-inheritance of a 3.7-kb α-globin gene deletion and SCD was associated with a late disease onset and possibly improved survival: there was a much higher allele frequency of the 3.7-kb α-globin gene deletion in SCD patients (40%) than in haemoglobin AA controls (10%). The data indicate the urgent need to develop and implement policy actions in sub-Saharan Africa on at least four levels: (1) the implementation of SCD screening practices and early neonatal follow-up; (2) the development and incorporating of socio-economic support to alleviate the burden of SCD on affected families; (3) the exploration of the appropriateness of the medical abortion laws for SCD, and (4) the development of national plans for genetic medicine, including research on genomic variants that affect the phenotypes of SCD, in order to potentially use them for anticipatory guidance.

Sickle Cell Anaemia in Central Africa: Environment, Genetics and Clinical features

Professor L.Tshilolo, L. Lucas, JP Gonzalez, G.Wamba and the REDAC group

Introduction
SCD is characterized by a variable phenotype expression depending on genetic and environmental factors. The more severe form seems to be related to people bearing the Bantu’s haplotype and living mainly in Central Africa countries.

The aim of the study
to contribute to the description of the natural history of SCD in Central African countries by determining the prevalence of sickle cell anaemia; the specific clinical data and the genetic and biological parameters.

Material and methods
Early diagnosis of SCA was performed by IEF, HPLC and /or Capillary electrophoresis in the some of REDAC’s countries (DRC, Gabon, Cameroon, Tanzania and Angola). Clinical and biological parameters were determined mainly in patients regularly followed up in DRC but also based on data published in the other REDAC’s countries.

Results
Globally, the prevalence of betaS gene in newborns was around 16% (AS) and 1.7 % (SS) with some differences according to the ethnic distribution and the prevalence of malaria.

Central African SCA patients displayed some specific clinical features: Hand foot syndrome, sepsis and acute anaemia were the early clinical signs; persistent of a large spleen was observed in 30-40% of patients aged >5yrs. Torrential nose bleeding, tooth decay and hypertrophic tonsillitis were frequent in young patients. Osteomyelitis was severe and often with multiple localization. Malaria was one of the cause of hospitalization in SCA patients; while clinical evident stroke seems to be less frequent (prevalence<5%) than what reported in the literature. TCD program have been recently introduced in some REDAC’s countries.

Hematologic parameters in SCA patients, in steady state, displayed a mean value of Hb at 7.2 g/dl and reticulocytes at 8.8%; a leucocytosis (14.9 g/L) associated with eosinophilia (7.8%) and monocytosis (14%). Mean value of HbF was around 8%. Alpha gene deletion (α-thal deletion) was observed in 39.5% of SS and 44.8% of AS. Among the AS, there was a trimodal distribution percentage of HbS corresponding to 2, 3 and 4 α genes respectively.

SCA patients from DRC displayed a permanent inflammatory and under nutrition status and developed high titres of auto antibodies.

Data from a cohort of 1229 children aged 0-5yrs showed that the introduction of specific vaccination (antihaemophylus and antipneumococcus) schedule and penicillin-prophylaxis reduced the blood transfusion rates to 40% and the risk of contamination by viral infections (HIV, VHB and VHC) from 10 - 15% to 5-8%. Hydroxyurea is progressively introduced in some of the Central African countries.

Conclusion
Knowledge of the natural history of SCD in Central Africa is one of the objectives pursued by the network REDAC in other to contribute to research and to sustain various projects on SCD control in Central Africa.
Gene-Disease Databases: Opportunities for advancing research, developing knowledge and improving patient care in sub-Saharan Africa

Dr Rosemary Ekong

Many genetic disorders now have a vast number of genetic variants identified as technology has advanced rapidly beyond what could have been imagined 10 years ago. Some questions often asked in diagnostic and clinical settings is “Does the variant identified in genetic testing cause the disease in the patient or, why are there different phenotypes in patients with the same genetic variant?” A tremendous amount of information is generated as a result of the need to understand the role of these genetic variants in disease, the consequences of cellular interactions between different gene products, the effects of external factors, and how all these contribute to the observed phenotype. With specialists and different institutions involved in each of these areas, information tends to be held in separate resources.

Africa bears a heavy burden of sickle cell disease (SCD) with a high frequency of the sickle cell haemoglobin (HbS) in Sub-Saharan Africa which causes sickle-cell anaemia. Despite HbS being due to a single nucleotide/amino acid change (GAG>GTG, p.Glu6Val) in the haemoglobin beta (HBB) gene, there is tremendous variability in the severity of the clinical presentation of SCD, and indeed sickle-cell anaemia. The reasons for such phenotypic variability are poorly understood. Various factors have been associated with the clinical variability in SCD and being able to establish specific factor-phenotype correlations would be of benefit to patient care.

There are publicly available databases on the HBB gene and some are no longer updated. HbVar (http://globin.cse.psu.edu/globin/hbvar/menu.html) is a global database for Haemoglobin Variants and Thalassemias that continues to be updated and contains not only variant information, but also the clinical presentation, biochemical and haematological information, and ethnic occurrence. Beginning to address the question of phenotypic variability, especially in Sub-Saharan Africa, would require a database that includes other factors such as socio-economic, environmental, infections, treatments and genes that have been identified to modify the clinical presentation of SCD. Choosing a database platform that can easily be adapted to the purpose and needs is important. I will show how we are using the Leiden Open Variation Database (LOVD) platform to address research and clinical questions, and how this is proving beneficial in the care of patients with the disease Tuberous Sclerosis. A similar approach for a multi-level HBB database will be discussed.
Evaluation of admissions to the Emergency Department of children with Sickle Cell Disease from 2006 to 2015 in Padova

Chiara Marra¹, Raffaella Colombatti², Laura Sainati², Liviana Da Dalt¹

Introduction: Sickle-cell disease (SCD) is a chronic multisistemic disease characterized by hemolytic anemia, susceptibility to infection due to spleen loss of function and vasoocclusive pain crisis in different districts. These patients have to be careful about the risk of acute complications and they need to access the Emergency Department (ED) in case of high fever, pain, respiratory symptoms or other acute emergencies.

In 2006 the World Health Organization suggested “to design (and) implement … comprehensive national integrated programs for the prevention and management of SCD” and the Italian Association of Pediatric Hematology Oncology (AIEOP) responded to this suggestion by organizing a SCD working group. Several meetings were held from 2008 to 2010 which led in 2012 to the publication of the Italian National Guidelines for the Management of children with SCD in Italy.

The Azienda Ospedaliera Università di Padova Hospital is a tertiary teaching hospital and its Clinic of Pediatric Hematology-Oncology (partecipating in AIEOP) began assisting patients with SCD in 2003. In 2006 a SCD Group specialized in taking care of children with SCD was created and a pathway of comprehensive care was organized. Since 2008 educational events were proposed for the personnel working in the ED (nurses, residents, attending physicians).

Objective
The main aim of this study was to describe the characteristics of the ED access by SCD patients and to evaluate the diagnostic-therapeutic pathway utilized by ED personnel for patients with SCD from January 2006 to July 2015.

Methods
This is a retrospective study which has involved SCD patients taken in care by the Clinic of Pediatric Hematology-Oncology of Padova Hospital and specifically those children who were admitted to the ED of Padova Hospital from January 2006 to July 2015.

The list of SCD patients was made available from the SCD Group of the Clinic of Pediatric Hematology - Oncology and information regarding demographics, SCD genotype, antibiotic prophylaxis and other chronic therapy was extracted from the SCD Database.

Data regarding the ED access, physical examination and laboratory tests, microbiological cultures or radiographic examinations were collected from the chart of the ED.

Information was collected in a Microsoft Office Excel file. Descriptive statistics were used to present data regarding patients, causes of ED access and the diagnostic-therapeutic pathways.

Moreover, the diagnostic and therapeutic pathways were compared before and after 2009. In 2008-2009 a series of educational events took place with residents and ED personnel on the acute management of SCD.
Results
General Information

66 patients (31 male, 35 female) with SCD were admitted to the ED from January 2006 to July 2015. 53 were HbS/HbS, 7 HbS/HbC, 4 HbS/HbB0 and 1 patient was HbS/HbB+.

94% of children came from immigrant families (83% African, 9% Albania and 2% Brasil) and only 6% were italians.

Mean age of the patients was 5.7 years (range 0-18 y) and the mean age at first visit in the ED was 5.4 years (range 0-17).

Mean age at diagnosis was 26 months (range 0-84 months) and 2 patients had prenatal diagnosis.

66 patients accounted for 393 accesses and mean visits/child was 6 (range 1-23). 13 patients (20% of all patients) accounted for 199 accesses (51%).

In 55 accesses (14%) related to 14 children the diagnosis of SCD was not already known; during 5 of this visits the attending physician suspected SCD disease.

The main reasons for admissions to the ED were: pain in 131/393 (33%), pain associated with fever in 93/393 (24%), fever in 76/393 (19%) and respiratory symptoms alone in 33 (5%).

The majority of patients indicated 1 painful site and the most frequently painful sites were abdomen (43%), limbs (40%), backbone (25%) and thorax (15%).

A high triage (yellow) was attributed in 55% of the admissions and in 65% of the admissions for patients with an established diagnosis of SCD.

During the medical history, information on vaccinations was recorded in only 16% of cases. Among the patients who had a known SCD status, information on antibiotic prophylaxis were recorded in 48% of visits, on folic acid in 23% of visits and on hydroxyurea in 20% of visits.

Pain
The Visual Analogue Scale (VAS) had been used in 52% of ED accesses for pain with fever and in 72% of ED accesses for pain.

Analgesic (or antipyretic) was administered in 66% of visits due to pain associated or not with fever. Only in 34% of visits analgesic was administered within 30 minutes.

Fever
Body temperature was taken in 96% of ED accesses in which reason was fever associated or not with pain. Blood culture was performed in 78% of visits due to fever. Only 5 blood culture were positive in the global period: 2 for Staphilococcus Aureus, 1 for Stafilococcus Capitis, 1 for Klebsiella and 1 for Salmonella Kingstone.

Antibiotic was administered in 44% of ED admissions and in 71% of SCD patients visits with temperature measured >38°C in ED.

The majority of antibiotic was administered as intravenous therapy (80%) and in the majority of cases it was a third-generation cephalosporin.

Respiratory symptoms
Chest X-ray was performed in 60% of visits due to thorax pain with or without fever or due to respiratory symptoms, or O2 saturation <96% during the physical examination.

In 31 visits O2 saturation had been found <96%: in 12 visits oxygen therapy was administered and in 14 visits a bronchodilatator was given.

The main diagnoses at discharge from ED were: vaso-occlusive crisis (36,3%), respiratory infection (19,0%), acute chest syndrome (11,5%), fever (13,4%), haemolytic crisis (6,4%) and 2 complication as spleen sequestration.

Outcome was admission to hospital in 181/393 patients (46%). One hundred thirty-one patients (34%) were discharged to home after 4-24 hour observation in the ED.

Comparison of ED admissions between and after 2009 showed an increased number of accesses due to pain without fever and a consequent increased of diagnoses of VOC (in 2006-2009: 32.0% vs 38.4% in 2010-2015).

A high score at triage (yellow) in general and to children with an established diagnosis of SCD was more frequent attributed (41% in 2006-2009 vs 61% in 2010-2015; p=0.0002) and the VAS score was more frequently utilised (13% in 2006-2009 vs 71% in 2010-2015; p<0.0001) in particular among patients with pain (26% in 2006-2009 vs 86% in 2010-2015).

During the medical history all the information were investigated more frequently after 2009: vaccinations (0% in 2006-2009 vs 16% in 2010-2015), antibiotic prophylaxis (22% in 2006-2009 vs 60% in 2010-2015), folic acid (15% in 2006-2009 vs 27% in 2010-2015), hydroxyurea (15% in 2006-2009 vs 22% in 2010-2015).

The number of blood culture performed in SCD patients with a body temperature > 38°C did not largely increase after 2009 (86% in 2006-2009 vs 88% in 2010-2015) but number of chest X-ray ordered in SCD patients with respiratory symptoms or O2 saturation < 96% increased (60% in 2006-2009 vs 73% in 2010-2015). Analgesic therapy was administered more frequently (44% in 2006-2009 vs 61% in 2010-2015; p=0.02) but waiting time for administration increased (60.9 minutes in 2006-2009 vs 92.6 minutes in 2010-2015). Antibiotic administration did not increase in SCD patient who had body temperature in triage >38°C. Oxygen therapy and bronchodilatators were given less frequent after 2010 with O2 saturation < 96%.

Conclusion
In the past decades we have observed an increasing number of children with SCD presenting to the Pediatric ED. Improvement in the management of children with pain, fever (main reasons for admissions to the ED) and respiratory symptoms have been recorded but major areas of concern remain mainly in the management of:

1 Pain: VAS score should be used in all patients and administration of the analgesics should be administered within 30 minutes from admission

2 Fever: blood culture and antibiotics administration should be performed in all patients with T>38°C
Neglect of sickle cell disease in Germany: The example of newborn screening

Dr Stephan Lobitz

Germany is proud to have become a country that welcomes immigrants and has therefore a moral obligation to serve their medical needs. However, there is an incomprehensible neglect of SCD, although the number of patients is rising continuously. SCD is neither an object in teaching medical students, nor in teaching doctors specializing in haematology and oncology. As a consequence of this deficit, medical care for patients suffering from SCD is not up to date in many places. To change this situation, the German Society for Paediatric Oncology and Haematology (GPOH) recently mandated an expert group (named “GPOH consortium SCD”) to develop a national disease management programme.

Without a doubt, newborn screening is a prerequisite for 21st century state-of-the-art SCD care and an important contributor to both, reduced morbidity and mortality. However, until now, the German newborn screening programme does not include haemoglobinopathies. Hence, adding SCD to the panel of target diseases of the German national newborn screening programme is one of the major tasks of the consortium. As the first step, the group has recently shown that at least in metropolitan areas, the neonatal prevalence of SCD is considerable, even though the disease only affects newborns with a familial migration background, but not the original German population. The data were convincing for both, the GPOH and the German Society of Newborn Screening. However, the final decision will be a political event with an uncertain outcome. The petition is currently in preparation.
The care of sickle cell patients in Italy: psychosocial issues and treatment availability

Dr Raffaella Colombatti

Sickle cell disease (SCD) is the most frequent hemoglobinopathy worldwide but remains a rare blood disorder in most western countries. It has emerged as an important health condition in Italy in the last decade due to immigration, mainly from Africa and Albania, and the number of affected children is steadily increasing.

The Italian Association of Pediatric Hematology Oncology (AIEOP) developed a national response to the rising number of SCD patients in Italy by creating a national working group focused on pediatric SCD, and publishing tailored guidelines for the management of SCD in Italy in 2012 (1). Efforts to deliver minimal standards of care across the country have been intensified in the past few years. Italy does not yet have a hemoglobinopathy newborn screening program, but several pilot programs have demonstrated the urgent need of universal SCD newborn screening (2-3). Multicenter Transcranial Doppler standardised training and screening programs have been implemented (4).

Neurocognitive evaluation, as part of comprehensive care, has been very challenging due to the social and cultural characteristic of the children, being mainly first generation immigrants from Africa with limited knowledge of Italian. The usual protocol of neurocognitive test was not sufficient to define multiple deficits experienced by children (5) and a broader evaluation was implemented. Results of multicenter surveys investigating language disabilities in immigrant bilingual children in Italy and of ongoing educational supportive programs will be discussed.

Hydroxyurea (HU) is widely recommended for treatment of children with SCD in developed countries, but information about its use comes mainly from studies performed in adults or in the United States. In Italy, children can receive HU free of charge from pharmacies or hospitals located near home upon presentation of the rare disease certificate and a HU prescription made by a physician. The only formulation available in Italy is the 500 mg capsule, not divisible.

A joint national survey on HU use in Italy was performed by the AIEOP and the Italian Society of Thalassemia and Hemoglobinopathies (SITE) in 2014. Preliminary results show that a significant number of children receive treatment (40%), the majority having begun HU after 2012, year of the National Guidelines publication. Some criticisms have been identified, mainly associated with no pediatric formulation available (low dose tablets or syrup), the relative high age of HU beginning (90 months), and a maximum dose lower than recommended (20 mg/Kg).

A better and standardised management of this relatively rare but complex disease, tailored to the population of SCD pediatric patients living in Italy and to our health system needs to be enhanced.

References
Impact of the use of Hidroxiurea in Children. Brazilian Experience

Professor Clarisse Lobo

Brazil is the largest country in South America, and the area is bigger than the whole of Europe. We have a population of one hundred and seventy million inhabitants irregularly distributed over the territory. Only 22% of the population has access to private health insurance and it is in our constitution that it is a universal right. That makes health a very important problem to be solved by the Brazilian Government.

Since 1988 Brazil has been building up a new health program. It is based on integrality, universality, equality and resolvability on health actions for all Brazilians, either employed or unemployed, during their whole life.

The main idea is to hierarchy and decentralize health actions which makes it more feasible and closely connected with the reality of the country. The programs are based on epidemiology data and must focus on preventive actions.

The health system will give full support for all the needs of health services from the most basic procedures to the highest level of complexity. Each facility is prepared for one level complexity as a net, on a hierarchy manner.

The whole system is supported by what we call social security budget and the money distributed according to the number of inhabitants and the level of complexity of the services in each area.

This system is called Sistema Único de Saúde, which means National Health System. Due to the poverty since 2000, Brazil must focus on public polices for black people. One that grows the most is SCD polices.

First National Hydroxiurea Guideline was published on June 2002 by Ministry of Health to be adopted by all centers in Brazil. Hydroxiurea is recommended for severe anemia, recurrent painful crisis, ACS, priapism and to recurrent stroke despite the use of chronic transfusion. It is also possible to consider the use of HU starting at age 3 regarding risks and benefits. The drug can be used as chronic medicine intake program for all patients who have good response and informed consent should be taken for all. According to that policy the use of Hydroxiurea grow almost 250% from 2008 to 2014.

Although evidence is accumulating that hydroxycarbamide decreases mortality among adults with sickle cell disease (SCD), there were no published data regarding the effect of hydroxycarbamide on mortality among children. The paediatric hydroxycarbamide program was established to treat children with scd ages 3-18 if they met disease severity criteria. Mortality data and clinical/laboratorial effects of hydroxycarbamide were retrospectively collected for the first 9 years of the program.

Mortality among those who received hydroxycarbamide was compared to that of untreated children. Among 1760 subjects, 267 received hydroxycarbamide at a median dose of 20.8 mg/kg/day (range 10-32) for a median of 2 years (range 0.1-6.5). Survival among hydroxycarbamide-treated children was significantly greater than that among untreated ones (99.5% versus 94.5%, p=0.01), due primarily to fewer deaths from acute chest syndrome and infection. Hydroxycarbamide therapy was significantly associated with increases in hemoglobin concentration, fetal hemoglobin, mean corpuscular volume, and reduction in platelets, reticulocytes and neutrophils. Toxicity was minimal and predominantly mild reversible neutropenia. Significantly fewer hospitalizations and emergency room visits, and shorter admissions were observed among hydroxycarbamide-treated subjects, when compared to the 12-month period prior to treatment initiation. Hydroxycarbamide therapy reduces disease severity and is likely associated with decreased mortality among children with SCD.

References


Poster Abstracts
Depressive Symptoms in Sickle cell disease patients and its impact on caregivers

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Introduction
Mental Health issues are growing at an alarming rate amongst sickle cell disease patients (SCD). SCD has a significant burden in Sub-Saharan Africa. In Nigeria, with asymptomatic carrier rate of 25% and disease prevalence of 3%, it represents a huge drain on health care service delivery. It is also the most prevalent genetic disease in the WHO African Region. In many countries, 10%-40% of the population carries the sickle-cell gene resulting in estimated SCD prevalence of at least 2% (1). Comorbid depression and other psychiatric disorders are common in people with SCD (2-4). The rates of depression are similar to those found in other serious chronic medical disorders, ranging from 18% to 44%, (5-7). A Nigerian study revealed a higher rate of depression in SCD subjects compared to those with cancer or malaria, but however lower than those with HIV/AIDS. (8)

This excess risk of depression and anxiety in SCD have been attributed to the chronicity of the illness; unpredictability of crises; chronic pain; overwhelming nature of medical complications, including anemia, fatigue, growth retardation, physical deformities, leg ulcers, renal failure, strokes, substantially reduced life expectancy; racial prejudice and stereotyping, social derision, disability, and financial stress (9) as well as stigmatization for pseudo-addiction to opioid analgesics. Depression and anxiety have been noted to be a predictor of daily pain and poorer physical and mental quality-of-life in adults with SCD, and account for more of the variability in the quality-of-life than hemoglobin type of SCD subjects.(2)

Comprehensive care of SCD depends on an appropriate contribution of medical care, non medical care and the cooperation of the affected persons. Affected persons in this context include the patient, family members, care givers and all involved in the patient’s health care (10)

Aims
This study aimed at determining the prevalence of depression and is associations among subjects with SCD in the University College Hospital, Ibadan as well as the impact on caregivers.

Methods
A descriptive cross-sectional study was carried out on patients with sickle cell anemia in steady state at the University College Hospital, Ibadan, Nigeria. Patient with family history of mental health, previous history of mental disorder or recent traumatic event were excluded from the study. Participants were assessed for depression using the (Center for epidemiological studies depression scale (CES-D) while caregivers were assessed for distress and preparedness for caregiving using the caregiving distress scale and caregiver preparedness for caregiving scale respectively. Other parameters assessed were; mobility and self-care, cognition, interpersonal activities of recruited patients. Comparison between depressed and non-depressed patients was performed using statistical univariate analyses followed by multivariate logistics regression.
Results

100 known SCA patients were recruited with a mean (SD) age of 17.3 (10.1) years and male to female ratio of 1.2:1. Depression (defined as CES-D score of 26 and above) was found in 66 (66%). Even though the rates of depression was higher in females than in males (66.7% versus 65.5%), the difference was not significant. However, the CESD score was observed to increase with increasing age (Rho: 0.218, p: 0.030). The occurrence of depression was not found to be related to disease severity as measured by rates of hospital admission, frequency of crisis, transfusion and leg ulcer. Worsening mobility, self-care and interpersonal activities were correlated with poorer CES-D scores (Rho: 0.20 – 0.37). There was a correlation between care givers preparedness for care giving and reported distress. Caregivers of patients with depression reported more distress compared to those of patients without depression (t: -4.15, p: 0.001). Multivariate analysis showed that caregiver’s preparedness, distress and patient cognition showed independent association with CES-D score (R²: 0.318, p <0.001).

Conclusion

Depression is a major problem with Sickle cell disease which is frequently overlooked by health care givers. More emphasis should be placed on psychological care of SCD subjects as well as their care givers as this will aid their comprehensive and holistic management. This will prove to be more economical and make for improved quality of life of those affected.

References

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A Comprehensive Descriptive Analysis of Racial and Ethnic Backgrounds within an International Cohort of Sickle Cell Disease Subjects: Implications for Disease Phenotype and Clinical Research

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Introduction

Millions are affected by Sickle cell disease (SCD) worldwide, with the greatest burden occurring in Sub-Saharan Africa. (Weatherall 2010) Its origin is thought to lie within the Malaria Belts of the world, and continues to affect thousands of lives on different continents, partly due to the migration patterns of the human race to different continents. In an effort to further understand the different phenotypes of SCD across the world, we created a SCD consortium across 3 Continents to compare the types of SCD and clinical profiles.

Aims and Objectives

To evaluate ethnicity and racial profiles of children and adults with SCD living in different environments.

Methods

The Consortium for the Advancement of Sickle Cell Research (CASIRE) group is an international multi-institutional collaborative group evaluating the clinical severity of adults and children with SCD through a validated questionnaire and medical chart review, standardized across countries. Patient ethnicity, including multi-generational information (country of birth of patient, patient's parents, and patient's grandparents) and racial background and ethnic region was recorded.

Results

At total of 781 patients were enrolled, 78% were Severe Phenotype and 22% were Mild Phenotype. 30% for patients were from U.S, 39% from Europe (25% United Kingdom, 14% Italy) and 31% from Ghana. A subanalysis of Ethnicity and Race was performed at most sites (UK was not included in all data analysis). There were 55% Female and 45% Male. While 99% of the Ghanaian patients reported their race as Black/African, Sickle Cell patients in Europe largely identified as Black/ African Descent (86%) followed by Caucasian (9%) and Middle Eastern (3.3%). The European cohort represented the largest group of Caucasian SCD patients (9%), with Italy comprising of largest percentage (17%). 91% of American patients identified as Black/African/African American, 4.1% Hispanic, 2.2% Caucasian, 1.1% Native American, 1.1% Middle Eastern. Further analysis of Ethnic Region revealed that West African Descent comprised the largest group of European patients (83%) with Nigeria (50.1%) and Ghana (12.8%) representing the largest percentage of this subpopulation. Conversely, Caribbean countries represented the largest Non-U.S. ethnic region of SCD patients at 14% followed by West Africa (9.9%). A sub-analysis of Ethnic Groups revealed Arab Descent SCD patients had the largest percentage of Mild SCD background (44%) while Caribbean Subjects revealed largest percentage of Severe SCD patients with 85%. A subanalysis also revealed although the patient may have been born in their respective country, a substantial percentage of patient's parents were born in a different country. While 68% of the SCD patients recognized Italy as their birthplace, only 10% of the mother and 12% of the fathers were also born in Italy. Surprisingly in the U.S. only 68% of mothers and 72% of father of SCD patients were born in America despite 89% of their children recognized the U.S. as their birthplace.

Conclusion: This is the first report of a comprehensive, multicenter analysis of ethnicity and race within an International/Transcontinental Cohort of Sickle Cell Disease patients. The diverse ethnic background observed in our cohort raises the possibility of how genetic heterogeneity within each SCD population subgroup can have implications on the clinical phenotype and clinical research outcomes.
Splenic dysfunction in sickle cell diseases: how well do we know the way it evolves?

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Introduction
The spleen is one of the most precociously damaged organs in sickle cell diseases (SCD). The slow circulation in this organ facilitates the deoxygenation of hemoglobin and therefore the sickling process. The consequence is repeated splenic infarctions leading to progressive splenic atrophy. This is the process that the literature describes as leading to progressive functional asplenia between 6 months and 5 years of age. [1; 2]

Objective: The aim of this study is to investigate the process leading to splenic dysfunction and its timing by means of scintigraphy, histology and immunohistochemistry.

Materials and Methods
All patients included in the study are followed at the Paediatric Haemato-oncology Clinic of Padova University Hospital. The 99mTc-labeled sulfur colloid liver-spleen (LS) scan of 21 paediatric patients affected by SCD was evaluated. The patients were selected because they were potential candidate to splenectomy in a population of 136 SCD paediatric patients. The histological characteristic of 4 spleens from SCD patients have been analyzed and compared to 5 spleens from HS patients, assuming that the spleen in HS patients is hyper-functioning and not damaged. For the immunohistochemistry analysis were used anti-CD8 and anti-SMA antibodies.

Results and Conclusions
The mean normalized LS ratio in SCD patients was above 20% for patients younger than 9. Even if splenic function is reduced and decreases progressively, it cannot be said to be absent at 5 years as asserted in the literature. [1; 2] At the histological exam the spleens from SCD patients showed a reduction of the lymphoid follicles, a distortion of the architecture and some regions of fibrosis, but no extended infarcted areas. The sinusoids appeared indefinite and the immunohistochemistry evidenced a reduction of CDB expression and an over-expression of reticular cells of the marginal zone. This alteration pattern reveals that splenic dysfunction in SCD might not only be caused by repeated acute splenic infarction related to vascular obstruction, but also by a progressive vasculopathy with sinusoidal damage, like in pulmonary hypertension, priapism, leg ulcers and cerebrovascular disease.[3] These findings show that medical understanding of the progression of splenic dysfunction is incomplete both in terms of the pathophysiological pathway and the timing. It is possible that both these elements are being modified by the chronic treatment that these patients now commonly follow. The main limit of this study is the small number of patients included.

Clinical Utility of Preemptive Genotyping of CYP2C19 allelic variants in Sickle Cell Disease

Cheedy Jaja

Background
Painful, acute vasoocclusive crisis (VOC) is the hallmark symptom of sickle cell disease (SCD) and is the precursor of diverse clinical co-morbidities affecting various organ systems, including cerebrovascular events, seizure, inflammation, infection, chronic depression, and chronic pain. Proton pump inhibitors, anticonvulsants, selective serotonin reuptake inhibitors, tricyclic antidepressants, and anti-infectives commonly prescribed for SCD co-morbidities are metabolized by the polymorphic CYP2C19 enzyme.

Aims & Objectives
We genotyped a SCD patient cohort to determine the frequencies of reduced, gain-of-function, or complete loss-of–function CYP2C19 variants that are associated with interindividual variability in drug response and adverse effects.

Methods
DNA isolated from whole blood of 165 unrelated SCD patients (82 males and 83 females, aged from 16 to 61 years) was genotyped for ten CYP2C19 *1, *2, *3, *4, *5, *6, *7, *8, *12, and *17 alleles across all study participants. Genotype profiles were generated using the iPLEX® ADME PGx multiplexed panel.

RESULT
Four CYP2C19 alleles (*1, *2, *12, and *17) were detected with the following frequencies 0.545, 0.209, 0.006, and 0.236, respectively. The predicted phenotype frequencies were distributed as extensive (31.5%), intermediate (24.8%), poor (5.5%) and ultrarapid (30.3%), and unknown metabolizer (7.9%) respectively.

CONCLUSION
This study provides important data on the pattern of CYP2C19 polymorphisms for the first time in an African American SCD cohort. For SCD disease related morbidities such as stroke, inflammation, infection, chronic pain and depression, preemptive genotyping of CYP2C19 variants could empower clinicians to communicate pharmacologic risk and drug response prediction with SCD patients using biological evidence as opposed to explaining statistical risk without biological significance. Further pharmacokinetic studies are necessary to determine the genotype - metabolic phenotype concordance in SCD patients due to the influence of disease state on CYP2C19 enzyme expression.

REFERENCES
Preemptive Genotyping of DMET Variants Involved In Opioid Analgesics Metabolism for Sickle Cell Disease Pain Management

Cheedy Jaja

Introduction
Interindividual variability in analgesic effects of opioids prescribed for sickle cell disease (SCD) pain is attributed to polymorphisms in drug metabolizing enzymes and transporters (DMET).

Aims & Objectives
We describe UGT2B7, SLC22A1, CYP3A4, CYP3A5, and CYP2B6 allelic variants characterized in opioid pharmacokinetic and pharmacodynamic pathways for determination of potential suboptimal opioid exposure in SCD patients.

Methods
DNA from 165 unrelated SCD patients was genotyped for 2 UGT2B7 alleles, 16 SLC22A1 alleles, 4 CYP3A4 alleles, 6 CYP3A5 alleles, and 7 CYP2B6 alleles using the iPLEX® ADME PGx multiplexed panel.

Results
We reported DMET genotype frequencies as homozygous wild-type, heterozygous, and homozygous variant/compound heterozygous; and predicted phenotypes as extensive, intermediate and poor metabolizers. We correlate deficient metabolic phenotypes with frequency of ED visits. Unwanted side effects of opioids due to impaired metabolic capacity may possibly be linked with higher likelihood of longer hospital stay.

Conclusions
The relationship between some DMET alleles, the metabolic index of opioids and their dose effects have not been evaluated presenting a crucial knowledge gap in the use of genetic profiling for opioid prescribing for SCD pain. Preemptive DMET genotyping would empower clinicians to communicate pharmacologic risk and drug response prediction using biological evidence as opposed to explaining statistical risk without biological significance.

References
Nutritional assessment of Sickle Cell Disease: four main components to consider

Claudine Matthews

Background
‘Under-nutrition’ is deemed by American researchers Hyacinth et al (2010), as a ‘critical feature’ of Sickle Cell Disease (SCD). SCD is a complex and multifactorial genetic blood disorder. Failing to acknowledge the mass of factors which impacts the health and psychosocial wellbeing of these patients would seriously hamper the accurate assessment of the nutritional risks of these patients, across their lifespan. Current tools assessing the nutritional risk of SCD patients are limited and do not consider the multifactorial nature of the condition.

Aim
To identify all the relevant components, influencing the nutritional needs of the SCD population affecting their nutritional risk; four main SCD specific components have been identified.

Method
The accurate assessment of the nutritional risk of SCD patients should include the following:
Nutritional considerations:
In addition to infection risk and dehydration; consideration should also be given to the ‘frailty’ risk (low mood, isolation, immobility) and gastrointestinal intolerances related to the condition.

Medical considerations
The symptoms encompassing a painful crisis, level and type of analgesia and choice of disease modifying treatment (Hydroxyurea, transfusion therapy and iron overload/chelation) should also be considered.

Wider determinants of health
The wider determinants of health including (poverty, housing, employment, ethnicity etc), which impacts the Quality Of Life (QOL) and life expectancy of SCD patients, should be considered.

Psychosocial considerations
How SCD patients perceive themselves and their condition should be factored in.

Results/Conclusion
A change in the nutritional management of SCD patients is long overdue! Careful consideration should be given to the multifactorial nature of the condition including the SCD specific factors affecting the nutritional risk of the patients. More research is needed to assess the efficacy of assessment tools currently used to assess the nutritional risk of SCD patients in the UK.

References
Nutrition in Sickle Cell: findings from a national Dietitians survey

Claudine Matthews

Background
Sickle Cell Disease (SCD) is an untapped specialism in Dietetics despite being the most common and fastest growing genetic blood disorder in the UK (Sickle Cell Society, 2008). Despite American Researches (Hyacinth et al, 2010) identifying under nutrition as a critical feature of the condition, nutrition remains underused and under recognised, as a viable management tool. Currently there are no SCD specific nutrition guidelines available, additionally dietetic involvement is limited for SCD.

Aim
The aim of the survey was to explore the levels of involvement, knowledge and attitudes of Dietitians of SCD in the UK.

Method
A link, to a 10 question self-administered online cross sectional questionnaire, was sent via the British Dietetic Association (BDA)s ezine newsletter as well as advertised on the BDA website, from April 2015.

Results
In total, 51 Dietitians responded; 89% from the London region. Overall, 96% of Dietitians agreed that they have a role to play in managing the nutritional needs of SCD patients, while 87% agreed that the condition warrants regular dietetic input. 85% identified the lack of adequate knowledge and understanding of the nutritional implications of SCD and 77% the lack of specific nutritional guidelines and standards of care for SCD, as factors that decrease dietetic involvement. In addition 84% agree that they have limited knowledge of SCD while 87% of Dietitians agree that SCD patients are not readily referred for dietetic input.

Conclusion
Dietitians have a significant role to play in managing the nutritional needs of SCD patients in the UK but without improvements to their knowledge and understanding of the specific nutritional implications of the condition, dietetic involvement will remain limited. Furthermore, improving dietetic engagement is dependent on the development of SCD specific nutritional guidelines; equally increasing referral rates of patients for dietetic input is essential.

References
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Thermal imaging in children with sickle cell disease: a pilot study of an educational tool

Attiya Khan (Medical Student), June Roberts (Community Haemoglobinopathy Nurse), Colin Michie (Consultant).

Background
Cooling of the peripheries can provoke a sickle cell crisis. It has been hypothesised that the reflex vasoconstrictor response to cooling is more marked in patients with sickle cell. Whilst some patients are aware of the need to stay warm, many are not.

Methods: We piloted the use of a thermal imaging camera (FLIR E60bx) in children with sickle cell disease both to detect clinical signs and as an educational aid. We invited 12 paediatric sickle cell patients in the clinics of a single west London hospital to participate during the summer of 2015. A short qualitative and quantitative questionnaire was used to initially identify patient’s knowledge of temperature and crises and whether they used extra clothing to keep warm. The camera was then employed to show patients thermal images of their hands, indicating areas of warmth and cold in colour. Pictures of non-sickle cell relatives were also taken to illustrate differences. The questionnaire was then applied to identify any changes in understanding relating to temperature and keeping warm.

Results
The pattern of heat distribution in patients did not appear different to non-sickle relatives (as shown by the pictures). A patient suffering dactylitis did not manifest significant differences in peripheral temperatures using this device. The results of the outpatient questionnaire showed that whilst most patients reported being affected by the cold weather (77%), few identified the cold as the cause of pain (42%). The majority of patients described the camera as a helpful educational tool, showing ‘heat’ and ‘temperature’. Many felt that the camera demonstrated a link between body heat and sickling pain, with 64% of participants saying that the camera would change their behaviour, by wearing more layers of clothing during future episodes of cold weather. This will be formally checked using the questionnaire and assessment of clothing in clinics through the winter.

Conclusions
This pilot study suggests that a thermal imaging camera is a particularly useful tool to help improve knowledge in sickle cell children with respect to preparing for cold weather.
Delayed but sustained engraftment following cord blood transplantation for Thalassemia Major

Nita Radhakrishnan, Anupam Sachdeva

Introduction
Stem cell transplantation has revolutionized the treatment of thalassemia patients worldwide. The availability of a matched donor is often the only hindrance to therapy even in the developing world. Related matched donor transplants in patients with no or minimal pre-transplant risk factors offer good results. Advancing age and non-availability of a suitable donor puts patients at significant risk even if they are well transfused and chelated. We describe hematopoietic transplant in a 8-year-old girl who received a single unit of matched cord blood stem cells and has remained well for the past 2 years.

Methods
8-year-old girl with Thalassemia Major was taken up for cord blood hematopoietic stem cell transplantation after exhausting options for family and unrelated bone marrow donors. She was Lucarelli Class II due to hepatomegaly and liver fibrosis re transplant. She was started on hydroxyurea for 4 weeks prior to conditioning to reduce the erythroid expansion. She received Fludarabine / Thiopeta/ Treosulfan conditioning following which matched (6/6) unrelated cord blood stem cells were infused. The cell dose of the cord blood unit was 2 logs less than expected as per the prestorage documentation of the stem cell bank. She received 0.19x 105 CD34 cells/micL. Since the cell dose was less, Methotrexate was omitted from the GVHD prophylaxis and she was continued on cyclosporine and GCSF was started from Day +4. Post transplant concerns included PRES, invasive Aspergillosis, CMV reactivation and Herpes reactivation over the next one year. Neutrophil engraftment was achieved on Day +79 and platelet engraftment on Day +90. Chimerism analysis was done on Day +73 which was 100% XY and since then 3 monthly for the last 2 years. Cyclosporine was tapered and stopped after a year of the transplant. Immune reconstitution is complete and she has been started on revaccination.

Discussion
Tolerability of HLA mismatch and reduced incidence of GVHD and easy availability make unrelated cord blood stem cells an attractive option for stem cell transplantation. It is however not an ideal donor source for benign hematological disorders due to concerns of dose and delayed immune reconstitution. Reduced dose of the stem cell product in our case resulted in delayed engraftment and reactivation of infections. However, she has remained well and has sustained engraftment since 2 years post transplantation.

References
Phenotypic variability of beta\(^0\) thalassemia: A single institutional experience

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Introduction
Beta thalassemia syndromes can present as thalassemia major, intermedia or minor. The genetic modifiers of beta thalassemia include the type of thalassemia mutation (\(\beta^0\), \(\beta^+\), \(\beta^{++}\)), secondary modifiers such as associated alpha mutations and Xmnl polymorphisms and tertiary modifiers such as hemochromatosis mutations\(^1\). In the present study, we observed the phenotypical variability of patients diagnosed with homozygous or compound heterozygous \(\beta^0\) mutations.

Methods
Retrospective analysis of patients diagnosed from 2010 to 2014 with beta thalassemia major/intermedia, with adequate follow up data and molecular diagnosis was done. Molecular diagnosis was advised only in patients who required a prenatal diagnosis or those with diagnostic dilemma. The age at first transfusion, age at diagnosis and frequency of transfusion was observed and correlated to the molecular diagnosis. Xmnl polymorphism was done in a select subset of patients.

Results
60 patients who fulfilled the inclusion criteria were analyzed. \(\beta^0\) mutations identified in these patients included IVS (1-1), IVS (1-5), Fr (8,9), 619bp deletion, Fr (41,42), Codon 30 G>C and Codon 16(-C). The median age at diagnosis of the cohort was 7.8 months (range: 2 months-11 years) and median age of first transfusion was 8.1 months (range: 2 months-11 years). There was no significant difference in the age of starting transfusions among the various molecular defects. 45 patients remained as thalassemia major requiring >8 transfusions per year. 15 remained non-transfusion dependent of which 2 have yet not received any transfusion at 6 and 7 years of age. Among the various genotypes, homozygosity for IVS 1-1 was associated with significant chance of non-transfusion dependent state (71.4%).

Xmnl polymorphism was observed in the homozygous state in 6 out of the 37 patients tested. The median age at transfusion in this subset was 3 years (6 months-7 years). There was significant difference in the age of diagnosis and age of first transfusion among patients who were wild type, heterozygous and homozygous for Xmnl polymorphism (p=0.003, p=0.002 respectively, Kruskal Wallis test). Testing for other modifiers such as alpha mutations and other polymorphisms were not done due to financial constraints.

Conclusions
Patients with apparently identical genotypes can have different clinical phenotypes. Phenotype-genotype correlation in beta thalassemia is complex and often requires testing for genetic modifiers at secondary and tertiary levels\(^2\).

References
\(^1\) Thein SL. Genetic modifiers of beta-thalassemia. Haematologica. 2005; 90(5): 649-60
Identification of Novel Imidazolylacryloyl Derivatives as Potential Antisickling Agents

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Background
Sickle cell disease (SCD) is an inherited disorder that affects millions of people throughout the world. Polymerization of sickle hemoglobin (Hb S) and the subsequent sickling of red blood cells (RBCs) that develop under low oxygen saturation conditions are exacerbated by the inherently low oxygen affinity of sickle RBCs – presumably as a result of increased intracellular concentration of 2,3-diphosphoglycerate in erythrocytes. This pathological process can be mitigated by increasing the oxygen affinity of Hb S, either by stabilizing the relaxed (R) state Hb and/or destabilizing the tense (T) state Hb. Covalent binding effectors of hemoglobin (Hb), such as aromatic aldehydes and ethacrynic acid (ECA) are known to exhibit these pharmacologic properties. The aldehydes form a Schiff-base with the N-terminal α-Val1 nitrogen at the α-cleft of liganded Hb, and through several inter-subunit mediated interactions tie the two α-subunits together to stabilize the R-state and increase Hb affinity for oxygen. ECA, on the other hand increases the oxygen affinity of Hb via a Michael addition reaction between its β-unsaturated carbon and the sulfur atom of βCys93, disrupting a T-state stabilization salt-bridge interaction, shifting the allosteric equilibrium to the R-state.

Aims and Objectives
Our objective is to develop novel antisickling agents based on the ECA pharmacophore and mode of binding to Hb, that we hypothesize would bind covalently to βCys93 of oxygenated Hb and destabilize the T-state in a similar fashion as ECA, but with more potent allosteric and antisickling activities.

Methods
We designed and synthesized several imidazolylacryloyl derivatives (designated as KAUS molecules). The in vitro effect of KAUS-38, KAUS-39, KAUS-15, KAUS-12, KAUS29, KAUS-33, KAUS-32, and ECA on increase in Hb O2 affinity or left-shift of oxygen equilibrium curves (OECs) were measured with multipoint tonometry using normal human blood at 37 °C. We further studied the compounds ability to inhibit erythrocyte sickling under hypoxia, as well as their atomic interactions with Hb.

Results/Conclusions
At 1 hour, KAUS-38, KAUS-33, KAUS-39, KAUS-28 and KAUS-29 (2 mM) quite significantly increased Hb affinity for oxygen (left-shifted the OEC by 14.2%-16.5%), while KAUS-32 and KAUS-15 only shifted the OEC by 7.4% and 5%, respectively. These results compare to 17.5% by ECA. KAUS-38, KAUS-39 and KAUS-15, when analyzed also showed time-dependent effect on the OEC, with the maximum left-shift of 24.1%, 16.7%, and 11.4%, respectively occurring at 4 hours, which compare to 30.1% for ECA. Interestingly, at 12 hours, the compounds still showed significant allosteric activity of ~15% for both KAUS-38 and KAUS-39, and 5.3% for KAUS-15, which compare with 20% for ECA. The compounds also showed inhibition of erythrocyte sickling when tested with sickle red blood cells at 2 mM, consistent with their ability to increase Hb affinity for oxygen. Crystallographical studies of deoxygenated Hb revealed an unpredicted mode of Michael addition reaction between the β-unsaturated carbon of the KAUS compounds and the N-terminal α-Val1 nitrogen at the α-cleft, while the corresponding liganded Hb structure appears to show the compounds interacting with βCys93 sulfur as observed with ECA.

We have developed novel compounds that are able to interact with Hb and increase the protein affinity for oxygen, and consistently decrease erythrocyte sickling. Most importantly, these compounds, unlike aromatic aldehydes appear to exhibit longer sustained action. The structural studies provide molecular level explanation to the biological activities of the compounds and offer a framework for targeted modifications to the KAUS molecules that would yield innovative and potent antisickling agents.
SCD (Sickle Cell Disease) in Azande living in the Nzara County, Western Equatoria State, Southern Sudan: preliminary results of haemoglobin studies on paediatric patients admitted to the Nzara TBI Leprosy Control Program and ARV Clinic

Cristina Tassi*, Sara Antonini, Federica Dassoni, James Kumbo, Isaiah Faustino, Romano Romai, Simonetta Nucci*.

Nzara TBI Leprosy Control Program and ARV Clinic, Western Equatoria- Southern Sudan and * SIMT Ospedale Infermi Rimini-AuslRomagna, Italy

Introduction and Background
SCD has been recognised as the most frequent inherited haemoglobin disorder in Sub Saharian regions. United Nations and WHO strongly recommend epidemiological and newborn or ante natal screening in these high risk populations. As regards to Southern Sudan, many tribes with high variations in their genomic assets, live mixed in contiguous regions due to bad security conditions and for this reason, any kind of epidemiological study is very difficult. In Western Equatoria state, the Azande represent the preponderant population and originate from the Bantu group of Zaire, a group showing a high incidence of Sickle Cell trait carriers and SCD cases. To date, in Southern Sudan rare data are available on hereditary hemoglobinopathies and in particular related to the Azande tribe.

Hospital Description
The Nzara TBI Leprosy Control Program and ARV Clinic is located in the Nzara County, Western Equatoria. The Hospital is run by the Diocese of Tombura and Yambio, under the medical direction of a missionary, Italian doctor. Overall activity is carried out by local personnel with a periodical assistance from Italian volunteers. The Hospital has been partially renewed and the paediatric department with 68 beds, has been activated in 2012. The TBC, Trauma, Medicine Departments host eighty patients, while one hundred out-patients are visited daily, 6/7 days per week. One thousand and eight hundred HIV patients are followed according to a WHO programme for ARV treatment and the Leprosy mobile clinic assists patients living in many villages far away. Every day, the hospital Pharmacy distributes the drugs prescribed by the hospital personnel. A Laboratory, functioning 6/7days per week and in case of emergency, performs main biochemical, haematological, parasitological tests and has been recently provided with a manual system for haemoglobin electrophoresis on agarose gel. The activation of a completely functioning blood bank is in progress: to date more than 200 units of blood are compatibilised per year and blood donors are tested for main blood groups and screened for viral, THPA and malaria infections before every donation.

Aims and Plan of the Study
This preliminary study has been conducted from November 2014 to July 2015, on children admitted to the paediatric ward for severe anemia and/or Malaria infection or showing clinical suspect of SCD. The main objective was to diagnose or confirm the hereditary defect to improve the treatment of sickle cell complications and to start with a long-term follow up and a prophylactic programme in SCD patients. Second aim was to describe the family incidence of the hereditary defect studying the blood relatives of patients found sickle cell trait carriers or affected from SCD. Finally, with this study we hope to test the feasibility of an extensive screening on children aged under 5, at high risk of death, newborn and pregnant females from families showing sickle cell trait carriers or SCD patients.
Patients, Materials and Methods
One hundred and sixty seven subjects entered the study. The majority of them were children suffering from repeated, acute Malaria attacks and severe anaemia or showing other clinical signs of SCD. Whenever possible, family studies were carried out and were completed in 16 families. All patients but three, were Azande living in the Nzara County. Haemoglobin (Hb) detection was limited to paediatric patients. In all cases but six, the first detection of pathological haemoglobin was performed by means of haemoglobin electrophoresis on agarose gel, employing the Hydragel Haemoglobin K20 kit. Then, samples in which a S band had been detected, the presence of the abnormal haemoglobin was confirmed with the same method using the Hydragel Haemoglobin Acid K20 kit. All materials and machineries for the Hb electrophoresis were purchased from Sebia Italia and the procedures were performed manually, following the indications reported in the products’ sheets. In limited cases, the Sickledex kit (from Streck, USA) was used to perform a sickling test according to the instruction contained in the data sheet. Finally, all data were registered in a specific form and in the patient’s file and recorded in a dedicated Excel data base adjourned at every patient admission. Basic data analysis was done when required (mean SD, T test for comparison between groups) using the statistical programme Statview.

Results
One hundred and sixty one patients were finally evaluable as in six cases data were incomplete, 120 were paediatric patients. One hundred and six children were hospital admitted as presented in table 1. Mean age of children was 5.5yrs. (0.1-13), being under 5 the 60% of the studied children. Regarding the 41 adults, 36 were blood relatives of SCD or sickle trait carriers. As regards to diagnosis, haemoglobin electrophoresis on agarose gel was performed in all patients but 7, in which only a confirmed positive sickling test was available. Twenty eight were the new diagnoses of SCD: electrophoresis results and incidence respect the number of patients studied have been shown in table 2. Mean haemoglobin value resulted significantly lower in SS subjects (4.8gr vs 6.7gr, p<.005) and at least, one unit of compatible blood was transfused in these patients. Among the 47 children admitted for an acute malaria attack and concurrent anaemia, 6 resulted sickle cell trait carriers and the -thalassemia was diagnosed in 3 cases. Family studies conducted in 16 families with one or more SCD patient or children sickle trait carriers, confirmed the expected presence of the sickle trait in the 50% of the brothers or sisters. Obviously both parents of SCD patients were sickle trait carriers and in one mother was newly diagnosed a previously silent SCD. At the moment, all SCD patients have been included in a long-term follow up and preventive treatment, with vaccinations and oral penicillin prescription. Moreover, 5 patients affected from severe SCD, have been submitted to Hydroxyurea (HU) treatment showing an overall, good compliance, and three more patients have accepted to start with HU.

Table 1: Patients admitted to paediatric ward

<table>
<thead>
<tr>
<th>Patients admitted</th>
<th>106</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria + anaemia</td>
<td>47</td>
</tr>
<tr>
<td>Severe anaemia</td>
<td>30</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1</td>
</tr>
<tr>
<td>SCD suspect</td>
<td>24</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 2: Haemoglobin electrophoresis on agarose gel

<table>
<thead>
<tr>
<th>PATIENTS</th>
<th>Number</th>
<th>Electroph.SS</th>
<th>SF</th>
<th>AS</th>
<th>AF</th>
<th>INCIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCD</td>
<td>28/161</td>
<td>5</td>
<td>23</td>
<td></td>
<td></td>
<td>1:5</td>
</tr>
<tr>
<td>A Thalassemia (children)</td>
<td>3</td>
<td></td>
<td>3</td>
<td>1:54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children Sickle trait carriers</td>
<td>17</td>
<td>0</td>
<td>17</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults Sickle trait carriers</td>
<td>28</td>
<td>0</td>
<td>28</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sickle trait carriers</td>
<td>45/161</td>
<td>23</td>
<td>45</td>
<td>6</td>
<td>1:4</td>
<td></td>
</tr>
</tbody>
</table>
Conclusion
This preliminary study has been conducted in a short period of nine months and due to many motivations, restricted to patients referred to the Nzara Hospital and their families. For the future, it will be beneficial, to extended the screening to children aged 1-2 and to newborn, as the incidence of the SCD in the Azande tribe seems to be significantly high. Despite the restricted number of the subjects studied, data seem to correlate to published epidemiological studies related to Zaire, from where probably, many Azande living in West Equatoria, originate. Finally, from a technical point of view, the detection of pathological haemoglobins by means of a manual Haemoglobin Electrophoresis on agarose gel, has been demonstrated feasible, despite the long time of preparation and execution in a laboratory extremely busy for the high number of samples to work in a restricted time. In the future, the availability of a partially-automated system that has been recently donated to the laboratory, might allow extensive studies, as, at the moment, these studies are feasible only in the Nzara Hospital.

Acknowledgements:
Our gratitude to Doctor Raffaella Colombatti for having reviewed the text and for her precious suggestions and to SEBIA Italia for the continuous technical support to this and future studies.
Retinopathy and vision loss in Haemoglobin SS and SC patients in Croydon University Hospital.

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Purpose
To assess the frequency of retinopathy and vision loss in patients with Haemoglobinopathy SS and SC.

Methods
Retrospective analysis of sickle cell retinal complications at Croydon University Hospital. The sample was comprised of 112 haematology patients (47 HbSC, 65 HbSS). Thirty-five SC (25 women, 10 men; mean age±SD, 43.2±8.9 years, range 29-61) and 30 SS (21 women, 9 men, mean age±SD, 35.8±10.5 years, range 19-60) patients had complete ophthalmology records. Visual acuity was measured using the Snellen chart. Retinopathy was evaluated by slitlamp fundal examination with dilated pupils and wide-angle fundus photographs.

Results
Corrected visual acuity was greater than or equal to 6/9 in both eyes in 90% of SS patients and 65.7% of SC patients; and less than or equal to 6/18 in the best eye only in one SC patient and none of the SS patients. Risk factors for vision loss were SC genotype and the level of retinopathy. Sickle cell retinopathy stages 0-2 (non-proliferative retinopathy) was found in 85% of SS and 30% SC patients, stage 3 (proliferative retinopathy) in 13.3% of SS patients and 40% of eyes from SC patients, stage 4 (vitreous haemorrhage) in 1 eye of 1 SS patient and 10% eyes of SC patients; and stage 5 (retinal detachment) in none of the SS patients and 20% of eyes from SC patients. Eleven eyes of 9 patients with stage 3 retinopathy had undergone laser panretinal photoocoagulation and 11 eyes of 7 patients (4 males, 3 females, age range 26-55) with stage 5 had had retinal detachment surgery (i.e. pars plana vitrectomy with our without gas/oil tamponade). The visual acuity after vitrectomy was 6/6 in one eye, 6/9 in 3, 6/12 in one, 6/60 in 3; and 2/60, hand movements and perception of light in one, respectively.

Conclusion
Vision loss is a rare complication of patients with Haemoglobinopathy SS and SC. Retinopathy is an important cause and advanced stages do not always respond well to available treatments. The pathogenesis and modifiable risk factors for sickle cell retinopathy are not well understood. Further research is necessary with the aim to develop strategies for the prevention and slowing the of retinopathy, such as treatment of disregulated systemic zinc homeostasis.
Dual therapy: hydroxycarbamide and automated red cell exchanges to improve sickle cell disease clinical phenotype

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Background
Hydroxycarbamide (HC) and regular automated red cell exchanges (auto REX) are the predominant effective sickle modifying therapies currently in use. Both modes of therapy have proven to be successful at reducing the frequency of vaso-occlusive crises and sickle associated complications such as acute chest syndrome, cerebrovascular events, priapism and venous ulceration (1, 2). Red cell exchange transfusion works by lowering sickle haemoglobin percentage (HbS %) levels, whilst reducing risk of iron overload whereas HC has several mechanisms of action but primarily increases foetal haemoglobin (HbF) levels and reduces expression of erythrocyte adhesion molecules. To date, there is limited data in the literature about the combined use, indications and benefits of offering both therapies simultaneously to patients with difficult to control disease and frequent crises (3).

Aims & Objectives
We set out to identify those patients with sickle cell disease (SCD) currently on dual sickle modifying therapies in the form of HC and auto REX at our Trust, a tertiary referral centre. Our aim was to study this population in terms of demographics, disease severity and indications (clinical triggers) for dual treatment. We report on the observed benefits including frequency of hospitalisation, pain intensity and HbS% suppression as well as the associated risks of dual therapy.

Methods
A retrospective analysis of patient data using clinic letters, blood test laboratory results and analysis of patient questionnaires to quantify patient experience and patient satisfaction were used.

Results
Out of a total of 6 patients on dual therapy we obtained the following results; Demographics: 5 females (83%), 1 males (17%), 3 patients aged 20-40 years (50%), 2 patients aged 40-60 years (33%) and 1 patient aged over 60 years (17%), 3 patients treated in a district general hospital and attending a tertiary centre for automated exchanges (50%), and 3 patients managed entirely at a tertiary centre (50%). Severity of disease: Documented SCD related complications: recurrent acute chest syndrome 1 patient (17%), painful venous leg ulcers 1 patient (17%), avascular necrosis of hip or shoulder 3 patients (50%), cerebrovascular event 2 patients (33%), and recurrent vaso-occlusive crises 6 patients (100%). All patients were commenced on dual therapy as a result of frequent hospital admissions and severe pain crises despite monotherapy with either HC or auto REX. Duration of dual therapy: 2 patients less than one year (33%), 1 patient between one and two years (17%), 3 patients between two to four years (50%). Reported benefits of dual therapy: frequency of hospital admissions: 4 patients report a documented reduction in hospital admissions (67%), whilst 2 report no change (33%). Severity of sickle pains: all 6 patients report a significant reduction in pain intensity and frequency of crises (100%). HbS% suppression: 4 patients (67%) maintain pre-exchange HbS% levels of less than 36% on 6 weekly exchanges, whilst 2 patients (33%) have on average pre-exchange HbS% levels of 50%, and 38.3% respectively. With regard to post-exchange HbS% levels, all 6 patients (100%) have levels of less than 16%. Of note, there were no additional reported side effects on dual treatment.
Conclusions
Despite the small number of patients in this project, we feel that the data provides an initial confirmation that dual therapy with HC and regular auto REX is a safe and well tolerated sickle modifying modality. This is a first step in assessing the benefits of dual therapy for selected patient groups which include reduced hospital admissions, reduced severity and frequency of crises alongside consistent and durable suppressed HbS% levels. The 2 patients with higher than expected pre-exchange HbS% levels can be attributed to infrequent exchanges for one patient not attending the recommended 6 weekly regime, and the other having recently started on auto REX and levels being monitored and correlated with symptoms initially. The patient questionnaires revealed an overall positive experience for patients with the majority stating a symptomatic improvement and benefiting from reduced hospital admissions and reduced frequency of crises. According to patients, these benefits outweighed the downside of dual therapy consisting in frequent hospital attendance and regular blood tests. Furthermore our data suggests that patients could be referred to tertiary centres for automated exchanges whilst continuing to receive their main sickle care input at their local centre simultaneously. Follow-on studies could focus on measuring the cost effectiveness of dual therapy and the associated improvement in quality of life. We highlight the need to explore the use of dual therapy further in selected patient groups in order to build more robust guidance for future use.

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A Systematic Review of Known Mechanisms of Hydroxyurea-induced Foetal Haemoglobin for Treatment of Sickle Cell Disease

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² Division of Hematology, Department of Clinical Laboratory Sciences, Faculty of Health Sciences, University of Cape Town, Cape Town, Republic of South Africa
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Short Title
Mechanisms of Hydroxyurea-induced Foetal Haemoglobin

Aims
To report on molecular mechanisms of foetal haemoglobin (HbF) induction by hydroxyurea (HU) for the treatment of Sickle Cell Disease (SCD).

Study Design
Systematic review.

Results
Studies have provided consistent associations between genomic variations in HbF-promoting loci and variable HbF level in response to HU. Numerous signal transduction pathways have been implicated, through the identification of key genomic variants in BCL11A, HBS1L-MYB, SAR1 or XmnI polymorphism that predispose the response to the treatment, and signal transduction pathways, that modulate γ-globin expression (cAMP/cGMP; Giα/JNK/Jun; methylation and microRNA). Three main molecular pathways have been reported: 1) Epigenetic modifications, transcriptional events and signalling pathways involved in HU-mediated response, 2) Signalling pathways involving HU-mediated response and 3) Post-transcriptional pathways (regulation by microRNAs).

Conclusions
The complete picture of HU-mediated mechanisms of HbF production in SCD remains elusive. Research on post-transcriptional mechanisms could lead to therapeutic targets that may minimize alterations to the cellular transcriptome.

Key Words
Sickle cell disease; hydroxyurea; foetal haemoglobin; Molecular mechanism; BCL11A, HBS1L-MYB and SAR1

The authors declare no conflict of interest.
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Guy’s and St Thomas’ NHS Foundation Trust
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