Search for a Cure for Sickle Cell Disease and Thalassemia Should be the Priority: YES!

Marsha J. Treadwell, PhD
13 October 2017
Arguments In Favor

- Hemoglobinopathies have a negative impact on quality of life for many affected individuals and families
- Disparities in quality of care and research for patients with SCD support the need to focus on curative therapies
- Success rates and improvements in quality of life as a result of curative therapies and impacts on utilization and costs could translate into improved efficiency and effectiveness of SCD healthcare worldwide
- Strategies to prioritize curative therapies for the hemoglobinopathies have been identified
11th Annual Sickle Cell Disease and Thalassaemia Conference 2017
Guy's and St. Thomas' NHS Foundation Trust

Yes the search for a cure should be the priority!

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Sherrie

- 27 yo female SCD HbSS
- From birth to transplant at age 11, almost 30 hospital admissions for acute chest syndrome, infections, pain
- Surgeries: cholecystectomy, tonsillectomy, splenectomy
- One of six sisters; parents, siblings and maternal grandmother with strong emotional bonds
- Multiple family stressors including a fire in the home around the time of the transplant and financial challenges with mother’s loss of employment
Sherrie

- Patient with cheerful demeanor and close relationships with hospital staff given multiple admissions
- Patient enjoyed art, writing and reading, but family members very physically active, e.g. camping and swimming
- Mother expressed guilt that patient was often alone during admissions due to father’s work and mother’s need to care for their other children and the household
- At time of transplant, patient and mother both with symptoms of anxiety and depression
- Stressor – recent death of another patient with SCD
Sherrie

- Eligible for transplant in 2002, with severe disease and a matched sibling donor
- In addition, patient AND family’s quality of life greatly diminished in relation to SCD diagnosis
- “I grew up in the hospital”
Impact of SCD and Thalassemia on HRQoL
Health Domains

- Physical mobility
- Mental health
- General health perceptions
- Bodily pain/discomfort
- Change in health
- Behavior
- School/Work functioning
- Family functioning

- Time, Emotional impact, Financial

- Patient-Centered
- Safe
- Effective
- Timely
- Efficient
- Equitable

Committee on Quality Health Care in America, IOM 2001
Quality of Life in Thalassemia

- Compared with U.S. norms, TLC patients (n = 264) reported worse HRQoL on 5 of 8 SF-36 subscales and on both the physical and mental health summary scores.

- Age, female gender and disease severity were associated with worse HRQoL despite longevity afforded by chronic transfusion therapy and iron chelation therapy.

- Over 1/3 of patients with thal intermedia in a smaller study (n = 48) reported poor HRQoL.

- While educational attainment was not problematic for over 600 patients with thalassemia in the TCRN, full time employment could be an issue.

Pakbaz et al Annals NY Acad Sci 2005:1054;457-461
Quality of Life in Sickle Cell Disease

- On PROMIS® measures, adolescents and females reported higher pain interference, depressive symptoms, worse physical functioning compared with younger children and males (n = 235)
- Scores worse in presence of AVN
- Scores significantly declined with hospital admissions (n = 121) and did not return to baseline at 2-3 weeks post admission


Impact of SCD on Health Related Quality of Life

Healthy children
African Americans in urban Milwaukee, WI
African Americans in Cincinnati, OH
Cancer: off treatment
Sickle cell disease
Cancer: on treatment
Severe obesity
Cystic fibrosis
Cancer
Asthma
Healthy adults
Sickle cell disease
Patients on dialysis

Adapted from: Panepinto J Hematology 2012;1:284-89
Psycosocial, Economic Burden of SCD

- 88% of parents (n = 130) of children with SCD surveyed in Cameroon reported moderate to severe difficulties coping.
  - Impacts from clinical severity, pain experiences, environmental stressors including parental unemployment, lower education, larger family size.

- Similar findings with 83 adult patients.

- In a study of over 400 adolescents and adults in Nigeria, societal stigmas were cited as problematic and over half of the sample reported depressed feelings.

- In the U.S. 30% of adults with SCD were on disability insurance and 50% were unemployed.

Anie et al Globalization and Health 2010; 6:2
Wonkam et al J Gen Counsel 2013; 23:192-201
Wonkam et al J Gen Counsel 2014; doi: 10.1007/s10897-014-901-z
Ballas et al JNMA 2010; 102; 993-9
Conceptual Model for HRQOL in SCD

Interventions
- Medical care
- Coping techniques

Pain
- Impact
  - Very Severe
  - Urgent/unpredictable

Emotional Distress
- Anxiety
- Depression
- Anxiety, depression about Health

Physical Distress
- Fatigue
- ADL/IADL Impact
- Stiffness

Role Interference
- Social
- Family
- Work (paid/unpaid)

Sickle Cell Disease

Key:
- ASCQ-Me
- PROMIS

Keller et al Health Qual Life Outcomes 2014;12:125
Pain in SCD and its Impact

- In the PiSCES study, pain was reported on 54% of days on daily diaries (n = 232 adults)
  - Severe pain episodes reported on 13% of days but health care utilization on only 3.5% of days
  - 29% of patients reported pain on 95% of days
  - Severe pain episodes remain a marker for risk of early mortality

Social Determinants of Health

- In SCD, poverty associated with
  - High prevalence of poor psychological adjustment
  - Academic underachievement
  - Unemployment
  - Increased utilization for acute events

- Exposure to neighborhood stress also contributes to diminished HRQoL

- Risks associated with poverty and illness are cumulative

Yarboi et al Child Neuropsychol 2015 Nov
Predictors of Neurocognitive Challenges

- 150 children 5 – 15 years screened for silent cerebral infarcts and completed assessments of cognitive functioning.

- Among 536 students 5 – 15 years, household income associated with grade retention while presence of SCI was not.

- For adults, cognitive impairment contributed to the risk of unemployment.

References:

King et al. Am J Hematol 2014;89:162-7
King et al. Am J Hematol 2014; 89: E188–92
HRQoL After Transplantation for SCD

17 pediatric patients with SCD who had undergone reduced-toxicity conditioning followed by allo-HCT (matched siblings and unrelated donors) and primary caregivers (n = 23) completed the PedsQoL 4.0 at baseline, 180 and 365 days post transplant.
HRQoL for Adults with SCD Post HSCT

- HRQoL scores for 9 of 12 engrafted adults post HSCT showed rapid and sustained improvement on the SF-6D from pre HSCT.
- Meaningful change (> .033) was seen at every time point.

Saraf et al. *Biology of Blood and Marrow Transplantation* 2016: 22; 441-48
Disparities in Access to Quality SCD Care and Research
Barriers to Quality Sickle Cell Disease Care

- Delivery system design
  - Lack of access to knowledgeable providers
  - Bias, discrimination and stereotyping
  - Poor care coordination
- Age related disparities
- Under-utilization of evidence based therapies
- Disparities in funding
  - Social determinants of health
Lack of access to knowledgeable providers

Bias, discrimination and stereotyping lower trust in healthcare system

Providers insensitive to SCD pain experiences and overly concerned about addiction, leading to failure to provide timely and adequate pain control when needed

In turn, negative health care experience may lead to postponement of seeking healthcare and self-discharge from the hospital

“Diagnosis profiling” – sickler, frequent flier
Under Utilization of Evidence Based Therapies

- Hydroxyurea as exemplar
  - Providers – concerns about patient adherence, lack of knowledge, concerns about side effects
  - Patients/Families – concerns about side effects, increased laboratory monitoring, obtaining prescription refills, HU as a “cancer drug,” masking of SCD symptoms, access to acute care
  - Systems – poor access to care/lower quality of care, lack of a medical home, limited access to comprehensive sickle cell centers, lack of care coordination, and poor transition from pediatric to adult care

Brandow, Panepinto *Expert Rev Hemato* 2010:3;255-260
Age-Related Disparities

- In population based studies, adults with SCD 18 – 30 years have highest inpatient and ED utilization and 30 day rates of re-admission.
- Pain episodes most frequent between 19 – 39 years of age.
- Dallas Newborn Cohort - 940 patients, 8857 patient years of follow-up - 7 new deaths occurred since 2002 – all in over 18 year age group and within 2 years of transfer.

Healthcare Utilization

Age at Death for People with SCD 2004-2008

Brousseau et al JAMA. 2010;303:1288-94
Quinn et al Blood 2010;115:3447-52
Paulukonis et al Pediatr Blood Cancer 2014;6:2271-6
Treating Sickle Cell Disease (SCD): The foundation of successfully treating SCD is screening children for the genes that cause SCD. Diagnosis and education are the next step, followed by vaccination, antibiotic treatment, and other disease prophylaxis. Beyond these foundational bedrocks, therapeutic approaches with hydroxyurea, blood transfusion, and potentially bone marrow transplantation can reduce common complications of SCD, increase life expectancy, and improve quality of life. (Figure used with permission from Dr. Hans Ackerman, NHLBI)
Understanding Barriers to Uptake of Potential SCD Public Health Interventions

- We used qualitative strategies to update or obtain information about perspectives on community attitudes and beliefs about SCD and sickle cell trait as held by stakeholders in Ghana, Cameroon and Tanzania

- Identified potential barriers to uptake of SCD public health interventions and participation in genomic research

- Focus on health and well-being of children and trust in clinicians and researchers, and driving force in families decisions to participate in research

Anie et al J Com Genetics 2016:7;195 - 02
Treadwell et al Omics 2017:21:323-32
<table>
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<tr>
<th>Category</th>
<th>Sample Statements</th>
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| Clinical Complications           | **Common symptoms are pain and anemia**  
| Chronic/Recurrent Illness        | **Child falls sick often**  
| Distinct Physical Appearance     | **Slim/thin**  
|                                  | **Yellow eyes**                                                                  |
| Misconceptions                   | **They think they can’t go to school**  
|                                  | **They think they cannot give birth**  
|                                  | **They…think it is from one parent only**                                        |
| Stigmatization                   | **Women with SCD are not advised to be married**  
| Superstition                     | **Caused by evil forces or spirits**                                              |
| Psychosocial Aspects             | **They just start crying. They know they are going to suffer with their babies**  
|                                  | **People think that it is going to end their marriage**                          |

Treadwell et al J Genet Couns 2015: 24; 267-77
Costs of Transplantation

In the U.S., it was estimated that there are 113,000 admissions annually related to SCD with an estimated cost of $488 million/year; with outpatient costs, $1.6 billion/year.
Prioritizing Curative Therapies

- Resources should be directed towards further optimizing HSCT approaches
  - Sherrie suffered with severe GVHD – in the 15 years since her transplant, procedure associated morbidity has been reduced
- HSCT for SCD should be made more accessible, including to patients without severe complications
  - Sherrie’s kidneys and lungs already damaged when she was transplanted
Yes the search for a cure should be the priority!

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Curative Therapies: Remaining Issues

- Patient/family barriers
  - Fears of transplant related mortality, morbidity; risk of long-term complications (GVHD/infertility)
  - Comfort with chronic transfusion regimens
  - Gaps in knowledge about natural history/progressive organ damage
- Health care provider barriers
  - Provider reluctance to recommend HSCT
  - Gaps in knowledge about role of HSCT

Benjamin Ethn Health 2011;16:447-63
Summary

- Hemoglobinopathies have a negative impact on HRQOL for affected individuals and families worldwide
  - Pain experience
  - Psychosocial burden
  - Associated environmental challenges including access to quality care and economic burden
- Given the success rates and improvements in quality of life associated with curative therapies, a patient centered approach dictates the need to offer patients/families this option early and as widely as is safe
Summary

- Disparities in quality of care and research for patients with SCD support the need to focus on curative therapies
  - SCD research has not advanced quickly enough in recent decades to address the devastating impact of the disease on youth and adults
  - Advances in care seem to have in fact decelerated for adults
- Curative therapy has demonstrated positive impact on healthcare utilization and costs
  - This could translate into improved efficiency and effectiveness of healthcare systems, particularly in low resource settings
Summary

- Despite phenotypic variability, SCD causes progressive damage beginning in childhood and HRQoL deteriorates over time.
- Supportive care focused on managing symptoms has not been very effective in allaying this progression.
- It is timely and equitable to offer curative treatment for individuals with “mild disease” who are nevertheless sustaining progressive organ damage.

Sheth et al Br J Hematol 2013:162;455-64
Support for Curative Therapies is Needed NOW!

- Better strategies to educate providers and patients/families about realities of untreated SCD and risks of transplantation are needed.
- Resources should continue to be channeled into new technologies and into perfecting existing technologies so that patients and families have options.
- Resources also needed on research that will help us more fully inform family, provider and public policy decisions regarding social, psychological and economic costs for patients and families.
Thank you!

- Mike Rowland, MPH
- Sherrie and her family
- The courageous families all around the world who are willing to take the risks that will advance science and ultimately, clinical care