

Interventions to Improve Appropriate Use of Therapies for Sickle Cell Disease

Abdallah Alomar*, Abdullah Ali Baawadh, Abdulkareem Alotaibi, Nour Abdulhamid Sadek, Samaher Mansi Alalawi, Afnan Hassan Mohamed Elsayed Hassan, Talib Wasil Al Jaredan, Alaa Ali Muri, Hamza Ahmad H Awad, Mohammad Mufleh Alharthi, Osama Noorullah Khojah, Meaad Mohammed Saeed Baatya, Abdulrhman Taj Uddin M Alsawas, Ameen Mohammed H Malky, Ali Ahmed Alawami and Abrar Omar A Eid

King Abdulaziz University, Jeddah, Saudi Arabia

*Corresponding Author: Abdallah Alomar, King Abdulaziz University, Jeddah, Saudi Arabia.

Received: February 17, 2017; Published: February 23, 2017

Abstract

Background: Sickle cell disease is a chronic and complex disease that demands a frequent contact with care providers. SCD is one condition in which negative health care provider attitudes are known to be prevalent and to affect the SCD patient-physician relationship, hence the need for a multidisciplinary intervention for pain management, transfusion and chelation therapy compliance, preventive and primary care issues, to patient education and education of other health care providers. to leverage educational intervention designed to improve health care provider attitudes toward patients with sickle cell disease (SCD).

Methods: The study group has synthesized studies that identified barriers to and interventions to improve appropriate use of these therapies through searching in MEDLINE and EMBASE, TOXLine and CINAHL considering papers starting from 1990.

Results: Thirty five studies have met the eligibility criteria for the systematic review and identified therapeutic barriers or facilitators. Thirteen studies evaluated interventions to improve use of therapies. Barriers to appropriate pain management were negative provider attitudes and lack of provider knowledge. Four of nine pain management interventions improved direct measures of pain management quality, while 5 improved indirect measures. One intervention improved receipt of routine ambulatory care.

Conclusion: Interventions to improve pain management in SCD can be effective and should address providers' negative attitudes and knowledge. Moreover, the availability of interventions of varying intensities provides greater flexibility in designing efforts to advance the quality of SCD care through the improvement of provider attitudes.

Keywords: Anemia; Sickle cell; Health care; Treatment; Intervention

Introduction

Sickle cell disease (SCD) is a group of genetic diseases which is especially prevalent in tropical and subtropical regions that have endemic malaria. Hence, SCD is most common in Africa, which accounts for an estimated 84% of worldwide affected births and has an average birth rate across the continent of 10.68 per 1000 live births [1]. Historical forced migration and ongoing population movement have spread SCD throughout the world, with estimated birth rates of 0.49 per 1000 in America, and 0.07 per 1000 in Europe, and 0.68 per 1000 in Southeast Asia. Within these continental regions there is a large variability in birth rate. The prevalence of carrier frequency is as equally variable with limited surveys reporting 1% to 38% in Africa, 0% to 29% in the eastern Mediterranean and 17% to 30% in India [2].

Prevalence of Sickle Cell Anemia in Saudi Arabia

According to a national wide community-based survey study done on 2008, Sickle cell disease was detected in 108 of 45,682 children and adolescents with a prevalence of 24 per 10,000. The regional distribution of sickle cell disease showed eastern region dominance with a prevalence of 145 per 10,000, followed by the southern region with a prevalence of 24 per 10,000, western region 12 per 10,000, and central region with 6 per 10,000. No cases were found in the northern regions. The male to female ratio was approximately 1:1 [3].

This study was further supported by another study in 2011, The prevalence of SCD in Saudi Arabia varies significantly in different parts of the country, with the highest prevalence is in the Eastern province, followed by the southwestern provinces. The reported prevalence for sickle-cell trait ranges from 2% to 27%, and up to 2.6% will have SCD in some areas. Clinical and hematological variability exists in SCD in Saudi Arabia with two major phenotypes: a mild phenotype and a severe phenotype [4].

Normal adult hemoglobin AA consists of two alpha and two beta globin chains. Sickle cell disease results from a single nucleotide switch of valine to glutamic acid in the sixth position on the β globin chain [5]. This may occur in one chain, resulting in the 'carrier' state of HbAS (sickle cell trait) or it may be coupled with another haemoglobinopathy, e.g. the thalassaemias. Substitution of both haemoglobin alleles with the 'sickle' variant results in homozygous SS disease, which is recognized as the most severe form of the group [6,7]. Life for individuals with SCD can be affected by repeated acute complications and compounded by progressive organ damage [8]. Many of these complications can occur in childhood. Stroke is a devastating complication of SCD during childhood or adolescence (or both). In people with homozygous SS disease, it has a reported incidence of 0.75 per 100 patient years in the two to five-year age group and a recurrence rate of 6.4 events per 100 patient years during a five-year period in people under 20 years of age [9]. Moreover, cognitive impairment has been linked to overt and silent infarcts in children [10]. Hyposplenism predisposes to recurrent infections with encapsulated organisms; and although greatly reduced by prophylactic penicillin therapy, infection still remains the leading cause of mortality in children with SCD [11]. Pulmonary diseases, including acute chest syndrome, are an important cause of morbidity and mortality in both children and adults with SCD [12]. Frequent vaso-occlusive crises are an unwanted trademark of the disease. They can become a major source of healthcare utilization leading to disruptions throughout an individual's lifespan and a reliance on healthcare professionals. As the life expectancy of people with SCD increases, they are more likely to suffer end-organ damage and present with complications such as renal disease, cardiac problems and retinal damage. The difficulty of adjusting to and coping with these various disease manifestations can often lead to reduced social interaction, anxiety and depression [13]. The unpredictable and varied pattern of complications results in uncertainties and a reduced quality of life for people living with SCD.

Methods

Scientific search database MEDLINE and EMBASE, TOXLine and CINAHL the search yielded 35 studies.

Inclusion criteria

Studies must be in English language and describe treatment of humans, and contain original data. For evidence of barriers to the use of recommended therapies among patients with SCD, we included 2 types of studies:

1. **Descriptive studies** (both qualitative and quantitative) in which patients, patients' caregivers, and health care providers reported their belief that a particular factor was a barrier
2. **Cross-sectional studies** in which a particular factor was identified as a barrier or facilitator through its association with use of an indicated therapy.

Data Extraction

We assigned primary and secondary reviewers; a primary reviewer abstracted the data, while a second reviewer checked the primary

reviewer's data abstraction for completeness and accuracy by reading the article and reviewing the primary reviewer's data abstraction form. Personnel included were with both clinical and methodological expertise. Differences of opinion were resolved by discussion between the reviewers through consensus adjudication by the entire research team. For all articles, reviewers extracted information on general study characteristics, participant characteristics, and types of barriers identified. For the qualitative studies, the reviewer categorized complex data. We have referred to a detailed systematic review study conducted by Haywood., *et al.* [14] for guidance on the methods used and concordance of results.

We ensured a direct link between the studies outcomes and outcomes of interest is established especially in the pain management interventions, for example, duration of hospitalization, costs, or emergency department "treat and release rates", and descriptive comments from patients (without an explicit analysis of those comments) to be a form of indirect evidence, and most chart abstracted measures of pain management quality (e.g., rates of patient-controlled analgesia or use of pain consults) and patient ratings of their experience to be a form of direct evidence. For each intervention study, we also determined by discussion if there was improvement, potential improvement, no improvement, or a detrimental effect. We categorized intervention studies as "improvement" if any measure of direct evidence showed statistically significant improvement and no outcomes (direct or indirect) worsened.

We categorized intervention studies as "potential improvement" if:

1. Improvements in direct outcomes with no statistical evidence.
2. 1 outcome measure at least (direct or indirect) improved and 1 outcome measure worsened.
3. Only indirect outcomes measures showed improvement.
4. The design of the study was through multivariate statistical techniques or standard epidemiological (risk of bias was not minimized) as with, health services, or qualitative design based techniques. We categorized intervention studies as "no improvement" if there was no improvement in any outcome and no outcomes worsened. We categorized intervention studies as "detrimental" if any measured outcomes worsened and no outcomes improved.

Data Synthesis

We did not attempt to quantitatively pool the data for any of the outcomes using the methods of a formal statistical meta-analysis because of the substantial heterogeneity among the studies in terms of their target populations of interest, study designs, and outcome measures.

Results

Data Synthesis

52 studies were identified that met the eligibility criteria, 35 of which were cross-sectional studies Identifying barriers or facilitators to therapy [32-34] and 9 studies evaluated interventions to improve use of therapies [35,36].

Detailed Description of Reported Barriers

Barriers reported by Patients

Some patients felt so disbelieved that they actively avoid consulting when in crisis, for fear of being perceived as opioid dependent. Many patients felt that doctors did not have sufficient knowledge of sickle cell disease to make valid treatment decisions.

Barriers reported by Staff members and Nurses

Several staff members stated that "patients were being denied proper medical care, unfairly accused of drug use or criminal behavior;

and generally being treated with less respect". With few exceptions the nurses' perceptions of their sickle cell patients were overwhelmingly negative.

While nurses believe cancer patients' self-reporting of pain, they generally believed that their sickle cell patients inflate their level of pain. 63% of nurses believed that drug addiction frequently develops in sickle cell patients and 49% reported that they did not have broad knowledge of sickle cell disease. 59% reported inadequate pain assessment tool was the greatest barrier in the management of pain episodes. Other barriers reported were lack of time for psychological support of patients (58%), nurse reluctance to provide opioids (37%), narrow range of available analgesics (37%), physicians' reluctance to prescribe opioids (33%), and the belief that most sickle cell patients are drug addicts (32%).

63% of nurses believed that drug addiction frequently develops in sickle cell patients and 49% reported that they did not have broad knowledge of sickle cell disease. 59% reported inadequate pain assessment tool was the greatest barrier in the management of pain episodes. Other barriers reported were lack of time for psychological support of patients (58%), nurse reluctance to provide opioids (37%), narrow range of available analgesics (37%), physicians' reluctance to prescribe opioids (33%), and the belief that most sickle cell patients are drug addicts (32%).

Barriers reported by Focus groups

patients report negative experiences of hospital care, characterized by mistrust (being suspected by health professionals of exaggerating pain), stigmatization (treated differently from other inpatients--"drug addicts"), lack of control (health professionals exerted control and failed to involve patients in decision-making), neglect (of personal care, monitoring of vital signs, psychosocial support).

Factors reported by the subset of 13 nurses who felt they could better relieve sickle cell pain were time, lack of knowledge of narcotic analgesia, fears of overdosing and addiction, and lack of experience with sickle cell patients. Most patients considered nurses' knowledge of sickle cell crisis and sympathy towards them as a patient group to be poor. Evidence of unsatisfactory pain management evidenced by comment from patient:

In 12 support group sessions of 2-8 patients each, patients all agreed on two major problem areas:

1. Obtaining appropriate medical care in the ER (long time to admission, feeling "forgotten", would delay hospital visits out of "dread").
2. Difficulty relating to members of the health care team (poor communication, "providers did not believe them", pain medication "not strong enough", discharged "too soon", being told "the pain is all in your head"). Also, patients noted lack of knowledge by providers and feel they are encouraged to 'act out' the pain in order to be taken seriously and medicated appropriately. Several group members said that "they would do everything possible" to keep from coming to the hospital because they dreaded it.

The 2 most common barriers identified by patients and providers were negative provider attitudes (13 studies) and lack of provider knowledge (5 studies). These negative provider attitudes included providers not believing that patients were genuinely in pain, providers being suspicious of drug abuse or addiction,36,41-provider stigmatization of patients with SCD,43,45 provider insensitivity or lack of sympathy50 and unspecified negative perceptions or attitudes.

It was concluded that the evidence was high and moderate that negative provider attitudes and poor provider knowledge, respectively, are barriers to use of appropriate pain medications during VOC (Table 1). The only consistent association with the use of prophylactic antibiotics was that patient sex was not associated with the use of antibiotics in any of the 3 studies in which it was examined. We concluded there was moderate evidence that patient sex was not related to use of prophylactic antibiotics (Table 1). Patient age, frequent hospital visits, and patient/caregiver knowledge were all studied in 2 or more studies, but the association of these factors to use of antibiotics was not consistent and all were given an evidence grade of low (Table 1). No factors were sufficiently and consistently studied or identified as barriers or facilitators to any of the other recommended therapies for SCD that we studied.

Type of Therapy	Factor	Barrier (n)	Facilitator (n)	Neither (n)	Evidence Grade
Prophylactic antibiotics	Patient/caregiver knowledge	0	2	1	Low that patient/caregiver knowledge is related to patient use of antibiotics
	Frequent hospital visits	0	1	2	Low that hospital visits are related to patient use of antibiotics
	Patient sex	0	0	3	Moderate that patient sex is not related to patient use of antibiotics
	Younger patient age	0	1	3	Low that younger patient age is related to patient use of antibiotics
Pain management during vasoocclusive crisis (VOC)	Negative provider attitudes	13	0	0	High that negative provider attitudes are a barrier to provider provision of pain medication
	Poor provider knowledge	5	0	0	Moderate that poor provider knowledge is a barrier to provider provision of pain medication

Table 1: Barriers and Facilitators to Use among Patients with Sickle Cell Disease to adhere to the appropriate therapy.

Interventions for Recommended Therapy adherence among SCD Patients

Nine intervention studies targeted providers to improve provision of pain medications to patients with VOC (Table 2).

Study	Study design	Study Location	N	Study Subjects	Main Intervention Components	Primary Outcomes	Improvement in Pain Management
Fertleman CR. [15]	Pre-post	London, UK	72	Children	Fast track admission Procedures	Pain management quality (time to analgesia delivery), patient ratings	Yes
Treadwell MJ. [16]	Pre-post	USA	235	Children	Clinical protocol	Pain management quality (staff use of validated pain assessment tools), patient ratings	Yes
Co JP. [17]	Pre-post, CCT	Baltimore, MD	369	Children	Clinical protocol	Pain management quality (use of IV fluids, incentive spirometry, and pain service consultation)	Yes
Mitchell MB. [18]	Pre-post	Philadelphia, PA	27	NS	Clinical protocol	Utilization ("treat and release" rates, length of stay)	Potential
Jamison C. [19]	Pre-post	Greensboro, NC	204	NS	Clinical protocol with staff sensitivity training	Patient ratings, utilization (length of stay), Costs	Potential
Cooper GS. [20]	Pre-post, CCT	Cleveland, OH	67	NS	Clinical protocol	Pain management quality (use of non-guideline narcotic meperidine), utilization (length of stay), costs	Yes
Benjamin LJ. [21]	CCT, Pre-post	Bronx, NY	144	NS	Establishment of day hospital	Pain management quality (decrease use of meperidine, increase use of hydro-morphone), Utilization ('treat and release' rates, length of stay)	Potential
Day J. [22]	Pre-post	UK	18	NS	Audit and feedback	Pain management quality (decrease use of intramuscular pethidine, increase use of patient controlled analgesia and pain consults)	Potential
Brookoff D. [23]	Pre-post	Philadelphia, PA	250	Adults	Clinical protocol	Utilization (#admissions)	Potential

Table 2: Studies on Provider Interventions to Improve Provision of Appropriate Pain Management during Vaso-occlusive Crisis. IV: Intravenous; NS: Not specified.

Studies design

- All used a pre-post design and 3 studies also had a concurrent control group.
- Three of the 9 studies included only children with SCD; 1, only adults; and the remainder did not specify.
- Seven of the 9 studies were conducted in the United States and 2 in the United Kingdom.
- The natures of the provider-targeted interventions were as follows: 6 of the interventions utilized a new clinical protocol to affect provider practice patterns, 1 involved conducting a retrospective audit of the quality of prior sickle cell care and providing feedback to providers on the results, and 2 involved changing the structure and organization of sickle cell care through use of a day hospital or a fast-track admission process.
- Only 1 study addressed provider attitudes through sensitivity training.
- Five of the 9 studies measured a direct outcome (e.g., pain management quality or patient ratings) while the remainder measured indirect outcomes (e.g., utilization or costs). Four studies demonstrated improvement
- 5 showed potential improvement.

This was considered as a moderate evidence that provider targeted interventions can improve appropriate provision of pain medications to SCD patients with VOC.

1. Study subjects refers to the group of patients with sickle cell disease who were the intended beneficiaries of the intervention. All of these interventions were targeted at health care providers who were therefore also study subjects.
2. To be categorized as “improvement,” a study had to demonstrate an effect on a direct outcome (pain management quality and/or patient ratings). Studies with a beneficial effect on indirect outcomes or where we thought there was a considerable risk of bias were rated as “potential improvement”.

Study characteristics and outcome

- Four studies evaluated the impact of patient interventions (**Table 3**):
- 3 of these attempted to improve self-management, such as adherence to prophylactic antibiotics (n = 1), desferoxamine (n = 1), and health-promoting activities (n = 1), and 1 study evaluated the effect of telephone outreach on utilization of routine ambulatory appointments.
- All 4 patient interventions were focused on children with SCD.
- None of the 3 studies to improve self-management had any effect, and we concluded that
- there was low evidence that patient adherence interventions do not improve use of therapies.
- The 1 study that used structured telephone outreach showed a significant and strongly positive effect on receipt of routine ambulatory care.

Study	Study design	Study Location	N	Study Subjects	Main Intervention Components	Type of Therapy	Relevant Outcomes	Improvement in Use of Therapy
Treadwell M. [24]	Pre-post	California	11	Children with SCD	Desferal day camp provided peer support and education for 4 days each summer	Desferal	Self-management (self-reported adherence)	No
Berkovitch M. [25]	RCT	Toronto	23	Children with SCD	Structured presentation of information to parents regarding antibiotic prophylaxis with weekly telephone calls from social worker	Antibiotic prophylaxis	Self-management (self-reported adherence)	No
Ketchen B. [26]	RCT	US, Canada	37	Children with SCD	Access to an internet-based program with weekly assignments of educational and social activities and those that encouraged child parent participation. Staff member called caregiver weekly	Health promoting activities	Self-management (self-reported adherence)	
Patik M. [27]	Pre-post	Pittsburgh, PA	202	Children with SCD	Telephone-delivered structured support and education by nonmedical personnel administered every 3 months	Receipt of scheduled care	Clinic attendance (% patients reporting having not attended clinic for 2 years)	Yes

Table 3: Studies on Patient Interventions to Improve Adherence to Medications and Receipt of Routine Care.

Discussion

Sickle cell disease (SCD) is one condition in which negative health care provider attitudes are known to be prevalent and to affect the SCD patient-physician relationship [28]. A systematic review of potential barriers to SCD care found substantial evidence to suggest that negative health care provider attitudes toward patients with SCD serve as a significant barrier to the delivery of appropriate pain management [28]. Examples of these negative attitudes are found in reports of adult patients with SCD that health care providers fail to show them respect by stigmatizing them as being “drug-seeking”, that providers often lack trust in them by expressing doubts about the veracity of the patient’s reports of their pain experience, and that providers do not treat the patient with SCD with a caring approach [28,29]. Although formal studies of these attitudes and experiences among youth with SCD are much more limited in number, the studies that can be identified document many of the same issues [30], and they comport with the experiences of youth with SCD who we talk to and care for in our own professional practices. Furthermore, parents of hospitalized children with SCD report many of the same difficulties in their experiences and relationships with health care providers as reported by adult patients. For example, parents of these young patients have been found to be more likely than parents of children hospitalized with other conditions to report an inadequate level of involvement in decision-making about their child’s care during the hospital stay. This result persisted even after controlling for the race of the parents [30,31].

Conclusion

There was moderate evidence that patient-targeted interventions can improve receipt of routine ambulatory care for SCD.

Bibliography

1. Modell B and Darlison M. “Global epidemiology of haemoglobin disorders and derived service indicators”. *Bulletin of the World Health Organization* 86.6 (2008): 480-487.
2. Weatherall DJ and Clegg JB. “Inherited haemoglobin disorders: an increasing global health problem [Inherited haemoglobin disorders: an increasing global health problem]”. *Bulletin of the World Health Organization* 79.8 (2001): 704-712.
3. Al-Qurashi MM, et al. “The prevalence of sickle cell disease in Saudi”. *Saudi Medical Journal* 29.10 (2008): 1480-1483.
4. Wasil Jastaniah. “Epidemiology of sickle cell disease in Saudi Arabia”. *Annals of Saudi Medicine* 31.3 (2011): 289-293.
5. Ingram VM. “Abnormal human haemoglobins. III. The chemical difference between normal and sickle cell haemoglobins”. *Biochimica et Biophysica Acta* 36 (1959): 402-411.
6. Pauling L. “Molecular disease and evolution”. *Bulletin of the New York Academy of Medicine* 40.5 (1964): 334-342.
7. Rees DC, et al. “Sickle-cell disease”. *Lancet* 376.9757 (2010): 2018-2031.
8. Stuart MJ and Nagel RL. “Sickle-cell disease”. *Lancet* 364.9442 (2004): 1343-1360.
9. Ohene-Frempong K, et al. “Cerebrovascular accidents in sickle cell disease: Rates and risk factors”. *Blood* 91.1 (1998): 288-294.
10. Steen RG, et al. “Cognitive Impairment in Children with Hemoglobin SS Sickle Cell Disease: Relationship to MR Imaging Findings and Hematocrit”. *American Journal of Neuroradiology* 24.3 (2003): 382-389.
11. Di Sabatino A, et al. “Post-splenectomy and hyposplenic states”. *Lancet* 378.9785 (2011): 86-97.
12. Scott Miller. “How I treat acute chest syndrome in children with sickle cell disease”. *Blood* 117.20 (2011): 5297-5305.
13. Anie KA. “Psychological complications in sickle cell disease”. *British Journal of Haematology* 129.6 (2005): 723-729.

14. Haywood C Jr., *et al.* "A systematic review of barriers and interventions". *Journal of the National Medical Association* 101.10 (2009): 1022-1033.
15. Fertleman CR., *et al.* "Evaluation of fast track admission policy for children with sickle cell crises: questionnaire survey of parents' preferences". *BMJ* 315 (1997): 650.
16. Treadwell MJ., *et al.* "Using quality improvement strategies to enhance pediatric pain assessment". *International Journal for Quality in Health Care* 14 (2002): 39-47.
17. Co JP., *et al.* "Does a clinical pathway improve the quality of care for sickle cell anemia?". *The Joint Commission Journal on Quality and Patient Safety* 29 (2003): 181-190.
18. Mitchell MB., *et al.* "Meeting the challenge of managing vaso-occlusive crisis". *Journal for Healthcare Quality* 24.56 (2002): 4-8.
19. Jamison C and Brown HN. "A special treatment program for patients with sickle cell crisis". *Nursing Economics* 20 (2002): 126-132.
20. Cooper, G.S., Armitage, K.B., Ashar, B. *et al.* Design and implementation of an inpatient disease management program. *Am J Manag Care.* 2000; 6: 793-801
21. Benjamin LJ., *et al.* "Sickle cell anemia day hospital: an approach for the management of uncomplicated painful crises". *Blood* 95 (2000): 1130-1136.
22. Day J. "An audit of pain management in acute sickle cell crisis". *Nursing Times* 93 (1997): 33-34.
23. Brookoff D and Polomano R. "Treating sickle cell pain like cancer pain". *Annals of Internal Medicine* 116 (1992): 364-368.
24. Elliott V., *et al.* "Parental health beliefs and compliance with prophylactic penicillin administration in children with sickle cell disease". *Journal of Pediatric Hematology/Oncology* 23 (2001): 112-116.
25. Berkovitch M., *et al.* "Trying to improve compliance with prophylactic penicillin therapy in children with sickle cell disease". *British Journal of Clinical Pharmacology* 45 (1998): 605-607.
26. Ketchen B., *et al.* "STARBRIGTH World: A pilot study of a home-based sickle cell psychoeducational intervention". *Child Health Care* 35 (2006): 321-338.
27. Patik M., *et al.* "Structured telephone-based outreach using nonmedical personnel can improve adherence to comprehensive care in families of children with sickle cell disease". *American Journal of Hematology* 81 (2006): 462-464.
28. Lanzkron S., *et al.* "Mortality rates and age at death from sickle cell disease: U.S., 1979-2005". *Public Health Reports* 128.2 (2013): 110-116.
29. Haywood C Jr., *et al.* "A video-intervention to improve clinician attitudes toward patients with sickle cell disease: the results of a randomized experiment". *Journal of General Internal Medicine* 26.5 (2011): 518-523.
30. Home Page. Initiative for Pediatric Palliative Care. (2014).
31. Rushton CH., *et al.* "Vision of hope: integration of palliative care in chronic pediatric disease" (2014).
32. Sox CM., *et al.* "Provision of pneumococcal prophylaxis for publicly insured children with sickle cell disease". *JAMA* 290 (2003): 1057-1061.
33. Hankins J., *et al.* "Therapy preference and decision-making among patients with severe sickle cell anemia and their families". *Pediatric Blood Cancer* 48 (2007): 705-710.

34. Zumberg MS, *et al.* "Hydroxyurea therapy for sickle cell disease in community-based practices: a survey of Florida and North Carolina hematologists/oncologists". *American Journal of Hematology* 79 (2005): 107-113.
35. Mitchell MB, *et al.* "Meeting the challenge of managing vaso-occlusive crisis". *Journal for Healthcare Quality* 24.56 (2002): 4-8.
36. Patik M, *et al.* "Structured telephone-based outreach using nonmedical personnel can improve adherence to comprehensive care in families of children with sickle cell disease". *American Journal of Hematology* 81 (2006): 462-464.

Volume 1 Issue 1 February 2017

© All rights reserved by Abdallah Alomar, *et al.*