Comparative Journal Club
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Asthma is associated with acute chest syndrome and pain in children with sickle cell anemia

Jessica H. Boyd, Eric A. Macklin, Robert C. Strunk, and Michael R. DeBaun

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Asthma is associated with Increased mortality in individuals with sickle cell anemia

Jessica H. Boyd, Eric A. Macklin, Robert C. Strunk, Michael R. DeBaun

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ABSTRACT

An analysis of a prospective cohort of individuals with sickle cell anemia (SCA), enrolled from birth through adulthood, was conducted to determine if asthma is a risk factor for death in SCA. All-cause mortality was determined for participants after adjusting for known risk factors for death in SCA. The study included 1,963 individuals who were followed for 18,495 patient-years. After controlling for established risk factors, individuals with SCA and asthma had a more than two-fold higher risk of mortality (hazard ratio 2.36, 95% CI 1.21 to 4.62, p=0.01). To summarize, asthma is a risk factor for death in SCA.

Key Words: sickle cell anemia, mortality, asthma.

Haematologica 2007; 92:1115-1118

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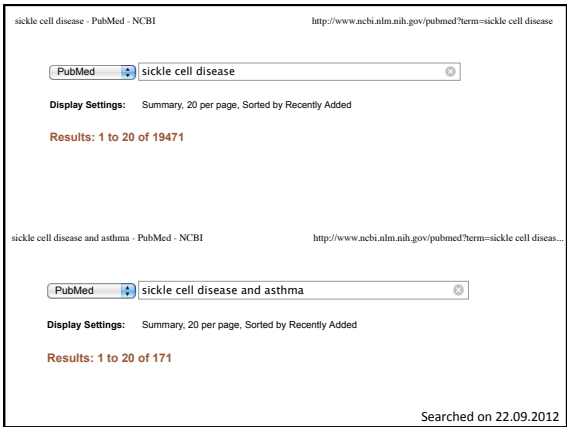

How to choose a paper?

- Subject / title: Does it sound relevant / interesting?
- Abstract: Could it be useful, is the study well-designed?
- Author list and institution: people known in the field?
- Journal: peer-reviewed, relevant to the field?
- Funding source(s)
- Time from submission to publication

Impact factors 2011

General Hematology

Top journals by impact factor	Impact factor
Cancer Cell	26.566
Journal of Clinical Oncology	18.372
Circulation	14.739
Blood	9.898
Leukemia	9.561
Cancer Research	7.856
Stem Cells	7.781
Haematologica	6.424
Journal of Thrombosis and Haemostasis	5.731
Blood Reviews	5.355
Thrombosis and Haemostasis	5.044
Journal of Leukocyte Biology	4.992
British Journal of Haematology	4.941
American Journal of Hematology	4.671

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What do these articles have in common?

- Exactly the same authors
- Data from the same study
- Two haematology journals relevant to the field
- Very similar subjects
- Almost the same references

Vol. 330 No. 23 LIFE EXPECTANCY AND RISK FACTORS FOR EARLY DEATH IN SICKLE CELL DISEASE 1639

MORTALITY IN SICKLE CELL DISEASE

Life Expectancy and Risk Factors for Early Death

Orah S. Platt, M.D., Donald J. Brambilla, Ph.D., Wendell F. Rosse, M.D., Paul F. Milner, M.D., Oswaldo Castro, M.D., Martin H. Steinberg, M.D., and Panpit P. Klug, M.D.

Abstract *Background.* Information on life expectancy and risk factors for early death among patients with sickle cell disease (sickle cell anemia, sickle cell–hemoglobin C disease, and the sickle cell–β-thalassemias) is needed to counsel patients, target therapy, and design clinical trials.

Methods. We followed 3764 patients who ranged from birth to 66 years of age at enrollment to determine the life expectancy and calculate the median age at death. In addition, we investigated the circumstances of death for all 209 adult patients who died during the study, and used proportional-hazards regression analysis to identify risk factors for early death among 964 adults with sickle cell anemia who were followed for at least two years.

Results. Among children and adults with sickle cell anemia (homozygous for sickle hemoglobin), the median age at death was 42 years for males and 48 years for females. Among those with sickle cell–hemoglobin C disease, the median age at death was 60 years for males and 68 years for females. Among adults with sickle cell disease, 18 percent of the deaths occurred in patients with overt organ failure, predominantly renal. Thirty-three percent were clinically free of organ failure but died during an acute sickle crisis (78 percent had pain, the chest syndrome, or both; 22 percent had stroke). Modeling revealed that in patients with sickle cell anemia, the acute chest syndrome, renal failure, seizures, a base-line white-cell count above 15,000 cells per cubic millimeter, and a low level of fetal hemoglobin were associated with an increased risk of early death.

Conclusions. Fifty percent of patients with sickle cell anemia survived beyond the fifth decade. A large proportion of those who died had no overt chronic organ failure but died during an acute episode of pain, chest syndrome, or stroke. Early mortality was highest among patients whose disease was symptomatic. A high level of fetal hemoglobin predicted improved survival and is probably a reliable childhood forecaster of adult life expectancy. (N Engl J Med 1994;330:1639-44.)

Table 5. Risk Factors for Early Death in Patients with Sickle Cell Anemia Who Were 20 Years of Age or Older.*

VARIABLE	VARIABLE ESTIMATE ±SE	P VALUE†
Fetal hemoglobin (%)	−0.09±0.04	<0.001
Acute chest syndrome‡	0.80±0.27	0.005
Renal failure	1.10±0.47	0.03
Seizures	0.91±0.42	0.04
White-cell count	0.10±0.04	0.01

*The values shown for the variable estimates reflect the associations between age-specific mortality risks and clinical profiles during the study in a multivariate model, with backward elimination, by proportional-hazards regression.

†Likelihood ratio, 1 degree of freedom.

‡Scored as follows: <0.2 episode per year = 1; ≥0.2 episode per year = 0.

CLINICAL TRIALS AND OBSERVATIONS

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Pain and acute chest syndrome (ACS) episodes are 2 of the most common causes of hospitalization in children with sickle cell anemia (SCA). However, very few potentially modifiable risk factors for either condition have been identified. In this prospective infant cohort study, we tested the hypothesis that asthma is associated with an increased incidence rate of pain and ACS episodes. An infant cohort was composed of 291 African American children with hemoglobin SS enrolled in the Cooperative Study for Sickle Cell Disease before age 6 months and followed beyond age 5 years. Asthma was defined by a physician diagnosis, an acute asthma event, or use of prescription asthma medications. The incidence rates of ACS and painful episodes were compared for children with and without asthma. A clinical diagnosis of asthma was made in 17% of the cohort. Asthma was associated with more frequent ACS episodes (0.39 vs 0.20 events per patient year, $P < .001$) and painful episodes (1.39 vs 0.47 events per patient year, $P < .001$). In conclusion, in children with SCA, asthma is associated with an increased incidence of sickle cell disease–related morbidity, including ACS and painful episodes. (Blood. 2006;108: 2923-2927)

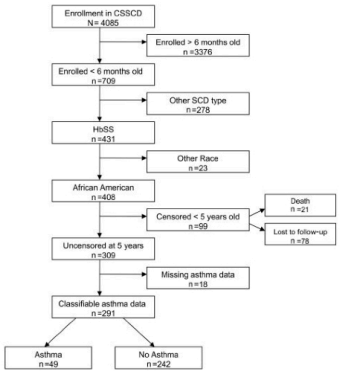

Figure 1. Enrollment in the infant sickle cell anemia cohort and eligibility for study cohort.

Table 1. Demographic features of patients with sickle cell anemia with and without asthma

	Asthma	No asthma	*P*
No. patients	49	242	
Sex, no. (%)			.27
Male	29 (59)	121 (50)	
Female	20 (41)	121 (50)	
Age at entry, mean (range), y	0.27 (0.29-0.50)	0.25 (0.22-0.50)	.48
Asthma Dx age, mean (range), y*	6.2 (5.0-11.7)	6.4 (5.0-11.6)	.29
Follow-up, mean (range), y†	11.7 (0-19.0)	10.9 (0-19.6)	.23
LAO by spirometry, no. (%)‡	13 (38)	9 (7)	< .001

*Age is the time when asthma diagnosis was first assessed.

†Follow-up is between date of entry and the earliest of transfer away from a study clinic, last routine study visit, last special study visit, initiation of chronic blood transfusion therapy, initiation of hydroxyurea, cerebrovascular event, bone marrow transplantation, or death.

‡Excluding 64 subjects (13 with asthma, 51 without asthma) with apparent restrictive disease.

Table 2. Clinical events in children with sickle cell anemia with and without asthma

	Asthma	No asthma	*P*
No. patients	49	242	
Acute chest syndrome (ACS), events per patient year	0.39	0.20	< .001*
Median time to first ACS, y	2.4	4.6	.01†
Pain, no. events per patient year	1.39	0.47	< .001‡
Transfusion, no. events per patient year	1.00	0.60	.02

*Incidence rates compared by negative binomial regression controlling for age at time of asthma diagnosis and lifetime average hemoglobin concentration, white blood cell count, and percent fetal hemoglobin.

†Median time to first event estimated by Kaplan-Meier, *P* value from Cox regression controlling for age at time of asthma diagnosis and lifetime average hemoglobin concentration, white blood cell count, and percent fetal hemoglobin.

‡Incidence rates compared by negative binomial regression controlling for age at time of asthma diagnosis, sex, and lifetime average hematocrit and percent fetal hemoglobin.

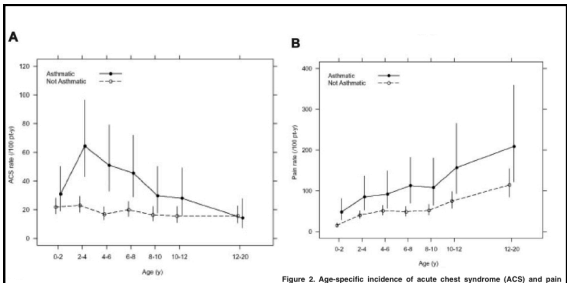

Figure 2. Age-specific incidence of acute chest syndrome (ACS) and pain events classified by clinical asthma status in the infant sickle cell anemia (SCA) cohort. (A) Overall incidence rate of ACS events is higher in children with SCA and asthma (0.39 events per patient year) when compared with children with SCA and without asthma (0.20 events per patient year; $P < .001$). (B) Overall incidence rate of painful events is higher in children with SCA and asthma (1.39 events per patient year) when compared with children with SCA and without asthma (0.47 events per patient year, $P < .001$). Line segments are point-wise exact 95% confidence intervals.

BRIEF REPORTS

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Key Words: sickle cell anemia, mortality, asthma.

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Table 1. Demographics of patients with sickle cell anemia that were evaluated for asthma.

	Asthma cases (n=138)	*Controls (n=1825)*	*p value*
Gender – no. (%)			
Male	65 (47%)	872 (48%)	0.93
Age at entry – yrs			
Mean	9.7	14.2	<0.001
Range	0.0 to 47.9	0.0 to 61.4	
Asthma Dx Age[1] – yrs			
Mean	14.0	20.2	<0.001
Range	5.0 to 53.9	5.0 to 67.4	
Follow-up[2] (yrs)			
Mean	10.8	9.3	<0.001
Range	3.0 to 19.6	4.6 to 19.8	

[1]Age is the time when asthma diagnosis was first assessed. [2]Follow-up for the cohort is between date of entry and loss to follow-up or death.

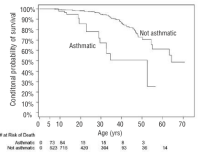

Figure 1. Kaplan-Meier plot of age of death for subjects with sickle cell anemia and asthma (n=138) and those without asthma (n=25) conditional on survival beyond age 5 years. Relative survivorship given here is conservative because asthmatic subjects were enrolled at younger ages and mortality risk increases with age.

Table 2. Cox regression estimates of mortality predictors, including estimates from both the final multivariate model and each predictor in a univariate model.

	N	*Multivariate Model Hazard ratio (95% CI)*	*p value*	*N*	*Univariate Models Hazard ratio (95% CI)*	*p value*
Age at study entry (yrs)	1828	0.779 (0.709,0.856)	<0.0001	2635	1.005 (0.956,1.057)	0.8496
Fetal hemoglobin (%)		0.929 (0.863,1.000)	0.0511	2407	0.916 (0.878,0.956)	0.0001
ACS rate (<0.2 yr^{-1} vs. ≥0.2 yr^{-1})		2.325 (1.267,4.265)	0.0064	2635	2.418 (1.799,3.249)	<0.0001
Renal insufficiency (Yes vs. No)		7.168 (3.687,13.936)	<0.0001	2635	3.922 (2.536,6.064)	<0.0001
Seizures (Yes vs. No)		1.275 (0.519,3.131)	0.5959	2635	2.405 (1.465,3.948)	0.0005
White-cell count (10^9/L)		1.182 (1.085,1.287)	0.0001	2566	1.107 (1.057,1.160)	<0.0001
Asthma (Yes vs. No)		2.362 (1.208,4.621)	0.0120	1963	3.855 (2.081,7.140)	<0.0001