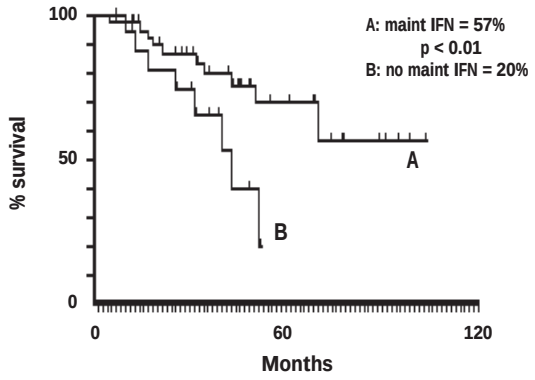

Figure 2. Progression free survival after first line IFN therapy, according to IFN maintenance therapy.

Zaja[9] also yielded similar results. A statistically significant lengthening of PFS was the result of IFN maintenance therapy, as already reported.[10]

Our experience, although limited, confirms the efficacy of purine analogs as second line therapy.

In agreement with Rai *et al*.[8] the very high projected survival probability of our series can be explained mainly by a two step therapeutic strategy made up of IFN first line therapy and purine analog salvage treatment for IFN resistant patients. Considering on the one hand our results and the reported good outcome of patients receiving IFN first,[7,8] and, on the other hand, the high CR rate and the prolonged survival obtained with front line purine analog therapy, the problem of defining a recommended first line therapy for HCL remains unsolved.

In conclusion, although the therapeutic emphasis in HCL has recently shifted to 2-CdA and DCF, IFN remains a therapeutic choice for this disease. We confirm that IFN is effective and tolerable and prolonged, reduced dosage administration may produce a long progression free period. We also confirm that achieving CR has no primary relevance in disease control and that good use of therapeutic resources may assure HCL patients a survival which is comparable to that of the normal, healthy population.

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Key words

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Screening for hemoglobinopathies in neonates in Argentina

Sir,

So far there is very little published information about the distribution of hemoglobinopathies in Argentina.[1] Historically the Argentine population is predominantly composed of individuals of Spanish, Aboriginal and mixed ancestry. There was an important wave of Italian immigration between 1876-1925, when 2,145,000 Italians arrived in our country, and another between 1947-1951 when a further 400,000 arrived. These immigrants settled especially in the provinces of Buenos Aires, Santa Fe, Cordoba, Mendoza and Entre Rios.[2] The population under study comes from the city of Rosario, in the south of Santa Fe.

One thousand unselected, umbilical cord blood samples collected with EDTA from consecutive neonates (Hospital Provincial del Centenario), were submitted daily to: identification of unstable hemo-

Table 1. Hereditary hemoglobin disorders in 1000 neonates.

Diagnosis	*Abnormal Hb (%)*	*N*	*Percentage (%)*
FA	–	993	99.3
FAS	8.0	5	0.5
Unstable-FA	2.9	1	0.1
FA-Bart	4.4	1	0.1
Total	–	1,000	100.00

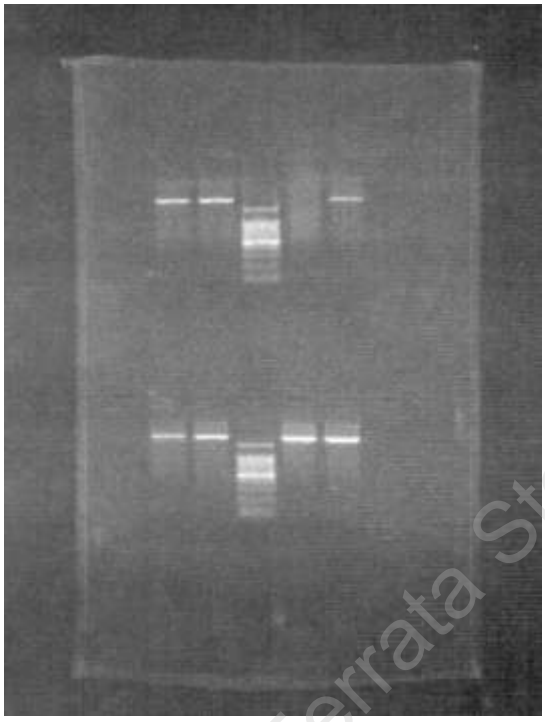

Figure 1 Detection of 3.7 Kb α-thalassemia-2 deletion by PCR. Lanes 1, 2: control α-thalassemia-2 (-3.7 Kb) heterozygote (αα/-α); lanes 3, 8: marker 100 bp ladder; lanes 4, 5: FA-Bart cord blood; lane 6, 7: father; lanes 9, 10: mother. Lanes 1, 4, 6, 9 using normal primers; lanes 2, 5, 7, 10 using specific primers for α-thalassemia-2 (-3.7 Kb).

globin by thermostability tests; detection of inclusion bodies. The hemolysate was analyzed by electrophoresis in alkaline and acid media. Whenever HbS was detected, induction of drepanocytosis was performed. The identification of chains by HPLC[3] was assessed in the unstable Hb. In the sample with Hb Bart, the presence of α^{+}Th was assessed by PCR.[4]

Data are presented in Table 1. The FAS phenotypes yielded a positive drepanocyte test, they were classified as heterozygous for Hb S, confirmed by family study.

An $\alpha^{3.7}$ homozygous deletion was identified, which was also detected in the proband's parents in a heterozygous state (Figure 1). The only positive unstable-FA was also detected in the neonates's mother (11%). It was electrophoretically silent, but with HPLC we determined that the anomalous chain was the β globin.

Cord blood screening is a useful tool for identifying sickle cell disease and α-thalassaemia. The population under study was Caucasian, and constituted mainly of individuals of Spanish origin, including a high percentage of mixed ancestry (Spanish-Aboriginal), and a minor proportion of individuals of Italian origin, and others. The early detection of HbS is of the utmost importance to reduce morbidity and mortality during the first years of life due to sickle-cell disease complications,[5] such as frequent infections. The risk of these complications increased even in heterozygous cases. Five HbS carriers were detected in our study: one of Italian ancestry and four of mixed ancestry. The observed heterozygote rate (1:200) is consistent with the gene frequency in the Mediterranean region.[6] The introduction of the gene S into our population is probably due to Spanish and Italian immigrants, since HbS in New World Amerindians has never been reported.[7]

In the newborn child (of Spanish ancestry) with Hb Bart the presence of an $\alpha^{3.7}$ deletion was investigated for, since this is frequent in Spain and Italy. It is probable that cases with the -α/αα genotype failed to manifest Hb Bart,[8] since the only positive result was homozygous (-α/-α).

Our results allow us to conclude that although screening studies in neonates are routinely carried out in several countries,[9,10] the low frequency of hemoglobinopathies detected in the present study does not justify these routine studies in our population. These results do, however, shed light on the prevalence of hemoglobinopathies in our region since up to the present time there are no published data on neonates in Argentina.

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Patients with venous thromboembolism have a lower APC response than controls. Should this be regarded as a continuous risk factor for venous thrombosis?

Sir,

Activated protein C (APC) resistance is characterized by a poor anticoagulant response to APC.[1,2] In most cases it is caused by the factor V Leiden mutation (FVLm) (1,691G→A).[3] Inherited APC-resistance has been found in 15-40% of thrombotic patients.[4] We report the APC-response of a group of thrombotic patients, the prevalence of APC-resistance and its thrombotic risk.

We studied 186 thrombotic patients (104 female, 82 male), referred to our Unit from January 1994 to March 1997. The clinical characteristics of the thrombotic individuals are shown in Table 1. The control group comprised 103 healthy blood donors (57 male, 46 female). Blood was collected 3-6 months after the most recent thrombotic event without influence of oral anticoagulants. APC-resistance was measured using a kit from Chromogenix (Möndal, Sweden). Antithrombin, protein C, S and lupus anticoagulant (LA) were also analyzed. Detection of FVLm was performed as described elsewhere.[3] Sex differences and influence of age were assessed by the chi-square test and correlation analysis. APC-ratios were compared by ANOVA, including age and sex as covariants. A logistic regression model was employed to estimate the odds ratio (OR), and to evaluate the risk of thrombosis associated with APC-resistance. The normal range was defined as the 2.5 and 97.5 percentiles (2.08-3.95). Patients had lower APC-ratios than controls (Figure 1) (difference after exclusion of APC-resistant individuals: 0.15, 95% CI: 0.03-0.27, $p<0.05$). Females had lower APC-ratios (difference after exclusion of APC-resistant individuals 0.20, 95% CI: 0.092-0.30, $p<0.0001$). No age influence was observed.

Patients with APC-resistance showed more than a five-fold increase in risk of thrombosis (OR 5.4; 95% CI: 1.8-16.4, adjusted for age and sex). A tendency towards an inverse relationship between the risk of thrombosis and the degree of APC-response was found [APC-ratio <2.08, OR 6.25 (95% CI: 2.01-19.42); APC-ratio 2.08-2.50, OR 1.82 (95% CI: 0.92-3.59); APC-ratio >2.5 was the reference interval].

Table 1. Clinical characteristics of the 186 thrombotic patients.

	n (%)
Sex	
male	82 (44)
female	104 (56)
Family history of thrombosis	77 (41)
Age at first thrombosis (mean±SD)	42.8±15.6
Spontaneous	67 (36)
Secondary*	119 (64)
orthopedic surgery	18 (9.7)
abdominal surgery	20 (10.8)
gynecological surgery	8 (4.3)
immobilization	8 (20.4)
pregnancy°	17 (16.3)
oral contraceptives°	14 (13.5)
varicose veins	12 (6.5)
neoplasms	8 (4.3)
others	15 (8.1)
Site of thrombosis	
deep vein thrombosis	109 (58.6)
pulmonary embolism#	53 (28.5)
superficial thrombophlebitis	14 (7.5)
upper arm thrombosis	5 (2.7)
mesenteric thrombosis	4 (2.2)
intracranial vein thrombosis	1 (0.5)

**Some patients had more than one risk factor (percentage of all cases); °only women were considered; #deep vein thrombosis was diagnosed in 36 patients with pulmonary embolism.*