The role of serum erythropoietin levels in diagnosis and classification of erythrocytosis/polycythemia

I read with great interest the recent paper of Gordeuk et al.[1] on congenital polycythemias/erythrocytoses, in which a diagnostic algorithm based on serum erythropoietin (Epo) concentration in non-phlebotomized patients is presented. As a first step the authors propose classification into primary erythrocytosis (increased red cell mass due to intrinsically abnormal bone marrow erythropoiesis) versus secondary erythrocytosis (excessive erythroid proliferation in response to pathological events outside the progenitor cells) according to whether the serum Epo level is below or above 5 IU/L.

Primary erythrocytoses are further distinguished into primary familial and congenital polycythemia (PFCP) and polycythemia vera (PV), the latter being acquired but occasionally occurring in a familial or juvenile context, whereas secondary congenital polycythemias can be subdivided into disorders of hypoxia sensing, conditions of increased affinity of hemoglobin for oxygen (hemoglobin mutants, 2,3-bisphosphoglycerate deficiency, methemoglobinemia) and congenital cyanotic heart or lung disease. The use of a unique clear-cut serum Epo level as classification criterion for primary *versus* secondary erythrocytosis, however, does not correspond to observations in a number of studies evaluating the discriminating value of serum Epo levels in polycythemic patients. Low serum Epo values have high specificity and moderate sensitivity for diagnosis of primary polycythemia compared with other erythrocytoses (Table 1).

Table. Studies evaluating the sensitivity and specificity of low serum Epo values for diagnosis of primary erythrocytosis in polycythemic subjects.*

	Diagnostic sensitivity (%)	Diagnostic specificity (%)	n_{tot}°	$n_{PE}$$
Available data for untreated polycythemic patients (at initial diagnosis)				
Mossuz et al.[2]	89	97	162	99
Shih et al.[3]	53	92	110	47
Remacha et al.[4]	60	99	190	43
Birgegard and Wide[5]	94	97	67	36
Available data for unselected (treated and untreated) polycythemic patients				
Messinezy et al.[6]	64	92	125	42
Messinezy et al.[7]	64 / 72§	99	130	42 / 36§

Only studies after 1990 are included because of limited accuracy and reproducibility of early Epo assays. °n_{tot}: total number of polycythemic patients in study. $$n_{PE}$: number of patients with primary erythrocytosis in study. §A single serum Epo estimation resulted in a low Epo level in 64% (27/42) of PV patients. When two samples were taken on different occasions, 72% (26/36) of PV patients had at least one low serum Epo value.

A normal serum Epo concentration does not exclude the possibility of PV[2-7] nor PFCP8, and even slightly raised Epo values have been observed in PV.[3] High serum Epo levels are most suggestive for secondary erythrocytosis but also occur in a significant proportion of patients with idiopathic erythrocytosis (increased red cell mass of unknown etiology after appropriate investigation) and apparent or relative erythrocytosis (raised packed cell volume but red cell mass within the normal range).[3,6,7] Despite considerable improvement in accuracy and precision of Epo assays, there remains an important overlap in serum Epo levels between primary and secondary erythrocytosis.[2-4,6,7] Thus, although a low serum Epo concentration is indicative of primary erythrocytosis and an elevated Epo level suggests tissue hypoxia, deregulated hypoxia sensing or autonomous Epo production, a normal serum Epo value is not discriminatory towards the origin of an absolute erythrocytosis. Serum Epo thresholds with a 100% predictive value for the diagnosis or exclusion of PV and secondary erythrocytosis were recently defined in a large multi-center study.[2] Serum cut-off values of 1.4 IU/L and 13.7 IU/L, determined with a commercial ELISA kit, allowed specific and direct diagnosis of 65.6% of untreated PV subjects (Epo < 1.4 IU/L) and 19.7% of patients with secondary erythrocytosis (Epo > 13.7 IU/L). More than half of the patients however displayed serum Epo levels between these two thresholds and could thus not be classified on the basis of serum Epo estimation alone.

As serum Epo values are known to be inversely related to hemoglobin (Hb) levels in normal individuals, it is important to consider the discriminating value of Epo levels in erythrocytosis in light of the Hb concentration. This relationship was investigated by Messinezy et al. in a series of 125 unselected, treated and untreated polycythemic patients.[6] The specificity of high Epo values for secondary erythrocytosis appeared to be less when the Hb concentration was not raised (< 16 g/dL), while low Epo values were less specific for PV at higher Hb levels (> 16 g/dL). The latter is in accordance with previous observations that after phlebotomy treatment to normal hematocrit levels, serum Epo levels increase in secondary erythrocytosis but remain usually low in PV.[3-5] The tentative diagnosis of primary erythrocytosis in case of a low serum Epo value at presentation should therefore be confirmed by redetermination of the serum Epo concentration after treatment.[6,9]

In conclusion, serum Epo measurement is mainly helpful for diagnosis of primary erythrocytosis but does not provide an absolute classification criterion for the majority of polycythemic individuals. Diagnostic evaluation of an absolute erythrocytosis should comprise a number of key investigations in all patients.[10] Additional tests can then be selected in a second stage to further clarify the cause of erythrocytosis. For the specific group of congenital polycythemias, which shows a much more restricted range of possible diagnoses than erythrocytoses in general, a rational and simplified work-up scheme has been recently proposed.[9]

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