

## ACHIEVING THE HEMOGLOBIN TARGET: A NOVEL APPROACH

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Attempts to achieve hemoglobin targets are futile without a clear understanding of the pharmacodynamics of ESAs. A 2-3 wk bone marrow lag needed to mature cells into reticulocytes and their variable survival (40-100 days) contributes to Hb cycling. The sum of these two processes is a natural lag which is not included in most dosing algorithms. We sought to define this lag accepting that any modeled lag in patients would also represent additional influences of iron stores and availability, demographic factors, and intercurrent events.

We extracted bimonthly Hb and thrice weekly i.v. EPO doses from our EMR in 30 HD patients. Individual Time Series of Hb and EPO were plotted using SAS v9.0. Each individual time series was examined for auto-correlation. After removing the auto-correlations (detrending/pre-whitening) the cross-correlation functions (CCFs) were examined. The positive lag at which the CCF peaks and/or achieves statistical significance represents the lag between EPO dosing and Hb response. A negative lag in CCF representing the feedback response of a change in the EPO dose by the treating physician to a Hb change can occur.

In these 30 patients, the CCF attained maximal values at variable positive lag periods (Range: 4 - 14wks.; mean  $\pm$  SD,  $8.5 \pm 2.9$ ). The lagged EPO series followed the Hb series closely. The mean lag of 60 days closely approximates the RBC survival in hemodialysis patients. An illustrative example with a lag period of 6 weeks is shown.

Using pharmacodynamics we show that the pharmacodynamics of EPO vary greatly amongst patients.

The lag intuitively suggests that one should avoid frequent EPO dose changes. We propose that this novel measure of the lag between EPO dose change and Hb response can be a useful parameter in EPO dosing strategies to minimize Hb variability.

